Medical Library

VOLUME 46 NUMBER 2

ARCHIVES OF INTERNAL MEDICINE

AUG 21 1930

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago
RICHARD C. CABOT, Boston
WARFIELD T. LONGCOPE, Baltimore
GEORGE DOCK, Pasadena, Calif.
WALTER W. PALMER, New York City
W. S. THAYER, Baltimore

AUGUST, 1930

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

CONTENTS OF PREVIOUS NUMBER

JULY, 1930. NUMBER 1

Frequent Chest Colds: Variability in Their Occurrence and the Bacteriology in Those Very Susceptible to This Type of Cold. I. Chandler Walker, M.D., and June Adkinson, A.M., Boston.

Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards: A Statistical Analysis. Walter C. Alvarez, M.D., Rochester, Minn., and L. L. Stanley, M.D., San Quentin, Calif.

The Metabolism of Obesity: VII. The After-Effect of Muscular Exercise on the Production of Basal Heat. Chi Che Wang, Ph.D.; Solomon Strouse, M.D., and Edith Smith, B.S., Chicago.

The Metabolism of Normal and Leukemic Leukocytes. Eugene C. Glover, M.D.; Geneva A. Daland, S.B., and Henry L. Schmitz, M.D., Boston.

II. The Diffusible Calcium and the Proteins of the Blood Serum in Malignant Diseases. Lewis Gunther, M.D., Los Angeles, and David M. Greenberg, Ph.D., Berkeley, Calif., with the Technical Assistance of John B. Dalton.

III. The Diffusible Calcium of the Blood Serum in Allergic Diseases. D. M. Greenberg, Ph.D., Berkeley, Calif., and Lewis Gunther, M.D., Los Angeles.

So-Called Malignant Hypertension: A Clinical and Morphologic Study. Francis D. Murphy, M.D., and John Grill, M.D., Milwaukee.

Primary Carcinoma of the Liver. G. F. Strong, M.D., and H. H. Pitts, M.D., Vancouver, Canada.

Chronic Arthritis: Bacteriology of Affected Tissues. Harry M. Margolis, M.D., and Anna H. E. Dorsey, M.S., Rochester, Minn.

Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis. Phillip F. Shapiro, M.D., Chicago.

Book Reviews.

Copyright, 1930, by the American Medical Association

Archives of Internal Medicine

VOLUME 46 AUGUST, 1930 NUMBER 2

THE VALUE OF ACID NEUTRALIZATION IN THE TREATMENT OF GASTRIC AND DUODENAL ULCERS *

WALTER LINCOLN PALMER, M.D.

CHICAGO

The treatment for gastric and duodenal ulcer has long been one of the most disputed subjects in the field of medicine. This situation is due to the fact that no method is entirely satisfactory, and yet all of the various procedures seem to possess some merit. A critical evaluation of their effect is difficult because of the characteristic tendency of the disease toward spontaneous remissions. In the majority of cases, little or no therapy is required to bring about a quiescent period.

The difficulty is increased by the lack of any definite objective means of determining when an ulcer has healed, except that of gastroscopy, a procedure not generally available, applicable or safe. The disappearance of the roentgenologic niche is sometimes considered to signify healing, but surgical experience has shown that an active ulcer may be found at operation even after the roentgenologist is no longer able to demonstrate a niche. The only other objective evidence of healing obtainable, the disappearance of occult blood from the stool, undoubtedly signifies a tendency toward healing but not complete reparation, for many ulcers are active and painful when they are not bleeding.

Subjective evidence of healing, i. e., freedom from distress, is no more reliable than the objective, for Berg [1] and others showed that the symptoms of ulcer subside even before the niche disappears roentgenologically. There is, then, aside from gastroscopy, no method of determining when an ulcer has healed or of measuring the rate of healing.

Gutzeit [2] noted that the first stage in the healing process is a subsidence of the inflammatory reaction about the ulcer. This is associated

* Submitted for publication, Dec. 23, 1929.

* From the Departments of Physiology and Medicine of the University of Chicago and the Cook County Hospital.

* This work was supported in part by grants from the Seymour Coman Fellowship Fund, and from the Douglas Smith Foundation for Medical Research, both of the University of Chicago.

1. Berg, H. H.: Die direkten Ulcussymptome des Ulcus duodeni, Ergebn. d. med. Strahlenforsch. **2**:251, 1926.

2. Gutzeit, K.: Die Gastroskopie im Rahmen der klinischen Magendiagnostik, Ergebn. d. inn. Med. u. Kinderh. **35**:1, 1929.

with or even preceded by a desensitization of the pain-producing mechanism, as is indicated by the rapid disappearance of spontaneous pain and the early transition from a positive to a negative "acid test." The pain of ulcer is due to the action of an irritant on a sensitive apparatus. The usual effective irritant and apparently the sine qua non of ulcer distress is free hydrochloric acid in adequate concentrations acting over adequate periods of time.[3] Failure of the irritant to produce distress under such conditions must be attributed to desensitization of the pain-producing mechanism. This change is indicated by the disappearance of spontaneous distress and by the transition from a positive to a negative "acid test." It apparenly represents an early step toward healing and hence may be used as a rough index of the rate of healing.

PROCEDURE

The purpose of this paper is to present data bearing on the rôle of free gastric acidity in the rate of healing of gastric and duodenal ulcer. In the experiments to be described, two groups of patients were subjected to substantially identical types of treatment except for the fact that in one, the so-called "alkali group," an effort was made to neutralize the free acidity throughout the entire digestive period, whereas in the other, the so-called "beef-tea group," gastric secretion was purposely stimulated in order to maintain as high a free acidity as possible. Conclusions were drawn regarding the results in each group by observing the rate of desensitization of the pain-producing mechanism.

The "acid test" was performed in the manner previously described [4] and is illustrated in the following protocols.

Patient 6007, a man, aged 37, entered the University of Chicago Clinics, Aug. 6, 1928, with a history of ulcer of three years' duration. Fluoroscopic examination revealed a definite deformity of the duodenal bulb with direct visualization of the crater of the ulcer.

The "acid-test" on Aug. 10, 1928, was as follows:

2:50 p. m.: Stomach aspirated; 40 cc. of liquid obtained. Free acidity, 31; total acidity, 46. No distress present. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

2:57 p. m.: Slight gnawing epigastric pain appears.

3:03 p. m.: Pain increasing, cramplike.

3:35 p. m.: Gnawing epigastric pain, identical in type and location with patient's typical distress, continues. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

4:12 p. m.: Typical distress continues. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

4:55 p. m.: Typical distress continues. Stomach emptied; 350 cc. of liquid. Free acidity, 93; total acidity, 99.

---

3. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcer, Arch. Int. Med. **38**:603 (Nov.) and 694 (Dec.) 1926; **39**:109 (Jan.) 1927.

4. Palmer, W. L.: The "Acid Test" in Gastric and Duodenal Ulcer, J. A. M. A. **88**:1778 (June 4) 1927.

5:12 p. m.: Slight gnawing pain still present.

Medical treatment was instituted August 13, with subsequent complete and almost immediate relief from distress. The examination by means of the x-rays was repeated September 1; at this time, a definite deformity of the duodenal bulb was seen, and the crater of the ulcer visualized again, although less definitely than at the previous examination. The "acid test," August 30, was as follows:

4:15 p. m.: Patient had no pain. Stomach aspirated.

4:20 p. m.: Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

5:06 p. m.: No pain. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

5:10 p. m.: Slight gnawing pain in region of navel.

5:21 p. m.: Distress ceases.

5:29 p. m.: Pain reappears.

5:36 p. m.: Distress ceases.

5:39 p. m.: Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

5:49 p. m.: Gnawing pain in region of navel reappears.

5:55 p. m.: Pain ceases.

6:10 p. m.: No pain. Four hundred cubic centimeters liquid aspirated from stomach.

The roentgenologic examination was repeated on October 12, revealing again a definite deformity of the duodenal bulb, but the crater of the ulcer was no longer demonstrable. The "acid test" on October 10 was as follows:

9:10 a. m.: No distress. Stomach emptied: 45 cc. of liquid. Free acidity, 60; total acidity, 63.

9:25 a. m.: Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

9:45 a. m.: No distress. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

10:15 a. m.: No distress. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

10:45 a. m.: No distress at all. Stomach emptied; 360 cc. of liquid. Free acidity, 108; total acidity, 110.

This case illustrates the manner in which the pain produced by the "acid test" may gradually lessen in severity and require a longer latent period for its production until finally the latent period exceeds the duration of the test, no distress occurs within the hour and a half of the observation, and the test is negative. Occasionally, one sees cases in which the change from the positive to the negative "acid test" comes suddenly, but usually it is gradual. The transition in this case roughly paralleled the disappearance of the crater as seen roentgenologically. Usually in gastric ulcer the test becomes negative long before the niche disappears entirely, and this seems to be true of the crater of duodenal ulcer, although in this type of lesion its disappearance cannot be followed as readily as in the larger penetrating niche of gastric ulcer. It is this transition, then, from a positive to a negative "acid test" and from spontaneous pain to no spontaneous pain, which has been used in

these experiments to indicate the rate of desensitization of the pain-producing mechanism, and as a rough index of the rate of healing.

The original plan was to assign alternately to two groups all of the patients with ulcer entering the Cook County Hospital, the only exceptions to be those with acute perforation or massive hemorrhage. It was soon found, however, that it was not practicable to carry out the experiment in this fashion among unsegregated ward patients; for this reason, one series was finished before the other was started. These two groups, known as the "alkali" and "beef tea" groups, were kept ambulatory and were treated alike in every respect, except as will be described later.

A number of the patients became free from symptoms within a few days after admission to the hospital, even though they were allowed to remain ambulatory and were given the general ward diet. The major-

TABLE 1.—*Groups Studied*

Alkali Group:		
Total number of cases		31
Released within 7 days		3
Acute appendicitis within 21 days		1
Cases studied		27
Gastric ulcer	3	
Multiple ulcers	1	
Duodenal ulcers	23	
Average duration of symptoms		6.1 years
Complicated by some obstruction, clinically		8
Later operated on		4
Beef Tea Group:		
Total number of cases		32
Released within 10 days		2
Intercurrent tuberculous pneumonia		1
Intercurrent carcinoma of the gallbladder		1
Mentally unreliable		1
Cases studied (all duodenal ulcer)		27
Average duration of symptoms		5.7 years
Complicated by some obstruction, clinically		8
Later operated on		1

ity of these became acid-insensitive also and consequently could not be utilized for study. The series under observation included, then, all of the patients with ulcer admitted to the wards for men during the experimental periods who had positive roentgenograms and remained sensitive to the "acid test" until the diagnostic study was completed, with the exception, of course, of those whose ulcers were complicated by acute perforation or massive hemorrhage. Five of them became dissatisfied during the course of the experiments and insisted on leaving the hospital within a few days. These were excluded from consideration, as were four who developed complicating conditions or who were discovered to be mentally unreliable. Table 1 summarizes the data on the groups selected and shows which cases in each group were discarded.

The alkali group comprised twenty-three cases of duodenal ulcer, one of multiple gastric and duodenal ulcer and three of gastric ulcer, whereas the beef tea group was composed of twenty-seven cases of duodenal ulcer. A comparison of the two groups might be criticized

because of this accidental difference, but such a criticism does not seem to me to be valid, for in my experiments there is no noteworthy difference between the response of the pain-producing mechanism of gastric ulcer to the usual forms of therapy, and that of duodenal ulcer. The two groups of twenty-seven cases may be regarded, I feel, as strictly comparable; for the average duration of symptoms and the frequency of outlet obstruction were practically the same in each. The fact that more cases were finally submitted to surgical measures in one group than in the other is of no significance, for various other factors were determinative in this regard.

TABLE 2.—*Scheme of Management*

Time, A. M.	Alkali Group	Beef Tea Group
7:00	90 cc. milk and cream	90 cc. milk and cream
7:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
8:00	90 cc. milk and cream 240 cc. cream of wheat	90 cc. milk and cream 240 cc. cream of wheat
8:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
9:00	90 cc. milk and cream	90 cc. milk and cream
9:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
10:00	90 cc. milk and cream 240 cc. of rice	90 cc. milk and cream 240 cc. of rice
10:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
11:00	90 cc. milk and cream	90 cc. milk and cream
11:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
12:00	90 cc. milk and cream	90 cc. milk and cream
P. M.	240 cc. custard	240 cc. custard
12:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
1:00	90 cc. milk and cream	90 cc. milk and cream
1:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
2:00	90 cc. milk and cream 240 cc. cream of wheat	90 cc. milk and cream 240 cc. cream of wheat
2:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
3:00	90 cc. milk and cream	90 cc. milk and cream
3:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
4:00	90 cc. milk and cream 240 cc. custard	90 cc. milk and cream 240 cc. custard
4:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
5:00	90 cc. milk and cream	90 cc. milk and cream
5:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
6:00	90 cc. milk and cream	90 cc. milk and cream
6:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
7:00	90 cc. milk and cream	90 cc. milk and cream
7:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
8:00	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
8:30	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
9:00	Entire gastric content removed, measured and titrated	
12:00	Stomach again emptied, contents measured and titrated	

Average daily dose of alkali: $NaHCO_3$, 26.3 Gm.; $CaCO_3$, 20.7 Gm.; MgO, 3.3 Gm.
Average daily dose of beef extract: 135 Gm.

The exact scheme of management used is shown in table 2. In both groups of patients, 90 cc. of milk and cream was given hourly from 7 a. m. to 7 p. m., together with five additional feedings of cereal or custard during the day. In the alkali group, alkaline powders were given in 90 cc. of water at hourly intervals from 7:30 a. m. to 7:30 p. m. and at 8 and 8:30 p. m. The powders consisted of calcium carbonate from 0.66 to 2 Gm. with sodium bicarbonate from 1.2 to 2 Gm., or heavy magnesium oxide 0.66 Gm. with sodium bicarbonate from 0.66 to 2 Gm. Occasionally, in cases in which an excessive night secretion existed, extra powders of calcium carbonate, 4 Gm., were administered between 9 p. m. and 12 midnight. If the evening aspiration revealed the presence of free hydrochloric acid, the hourly dose of alkali was increased, although in a few cases

even the largest powders failed to bring about a state of continuous anacidity. It was assumed that the 9 p. m. titration was an index of the peak of the daily acidity. The validity of this assumption may properly be questioned, but nevertheless it must be admitted that the average total daily dose of alkali, 26.3 Gm. of sodium bicarbonate, 20.7 Gm. of calcium carbonate and 3.3 Gm. of heavy magnesium oxide probably neutralized a large proportion of the free hydrochloric acid secreted during the digestive phase. The stomach was emptied of its entire content every night at 9 p. m. and again at 12 midnight.

In the beef tea group, hourly doses of 90 cc. of 10 per cent Liebig's beef extract, the secretogogue property of which has been shown by Pavlov [5] and Ivy and McIlvain,[6] were substituted for the alkali and water of the alkali group. This was done in order to stimulate gastric secretion and accentuate the difference in the free acid levels in the two groups. Milk and cream neutralize large quantities of hydrochloric acid, as was shown by Senator,[7] later by Bönniger,[8] and recently by Freezer, Gibson and Matthews.[9] This effect was desirable in the alkali group, whereas in the beef tea series it had to be counteracted if the maximum contrasts were to be obtained in the free acid levels of the gastric content. It was thought that this could be accomplished best by the hourly feeding of beef tea.

Chart 1 shows a comparison of the effect on gastric secretion of water with that of 10 per cent Liebig's beef extract. The stomach was emptied per Rehfuss tube, then 100 cc. of water was injected; an hour later the stomach was again emptied, another 100 cc. of water injected, etc. The curve represents the free acid level. On another day, the experiment was repeated, 100 cc. of beef extract tea being used instead of water. The free acid curve is higher.

Chart 2 portrays a similar experiment carried out in one ten hour period. It is assumed in the later experiments that continued hourly administrations of beef extract resulted in continued stimulation of the secretory mechanism, but the possibility exists that this was not the case. It was not possible to know the exact level of gastric acidity minute by minute or hour by hour from day to day in any patient in either group, but there is reason to think that a definite difference in acidity between the groups existed. This hypothesis is supported by the fact that the average free acidity of the beef tea group at 9 p. m. was more than double that of the alkali group (table 5). The period of

5. Pavlov, J. P.: The Work of the Digestive Glands, London, Charles Griffin & Company, Ltd., 1902.

6. Ivy, A. C., and McIlvain, G. B.: The Excitation of Gastric Secretion by Application of Substances to the Duodenal and Jejunal Mucosa, Am. J. Physiol. **67**:124, 1923.

7. Senator, H.: Ueber die diätetische Behandlung des Magengeschwürs, Deutsche med. Wchnschr. **32**:95, 1906.

8. Bönniger, M.: Zur Diagnosis des Ulcus ventriculi, Berl. klin. Wchnschr. **45**:396, 1908.

9. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: A Contribution to the Study of Alkalies as Therapeutic Agents, Guy's Hosp. Rep. **78**:191, 1928.

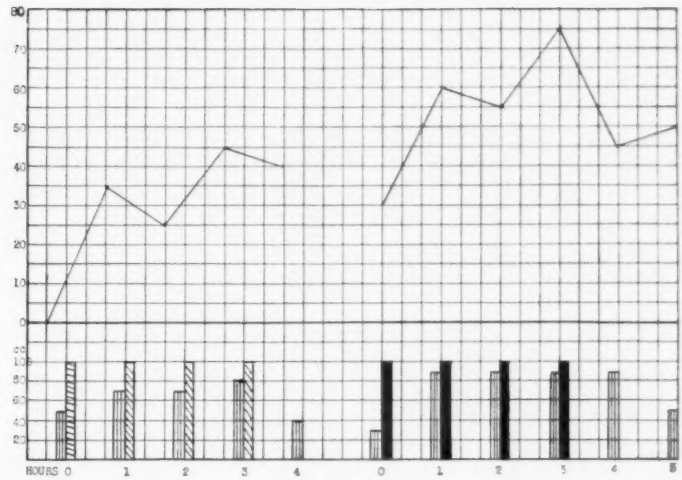

Chart 1.—A comparison of the effect of water with that of 10 per cent beef extract on gastric secretion. The curves represent the free acidity of the gastric contents. In the lower section of this chart and chart 2, the vertical lines indicate the amount of gastric contents removed; the diagonal lines, the amount of water injected, and the solid figure, the amount of beef extract tea injected. An interval of days occurred between the two determinations.

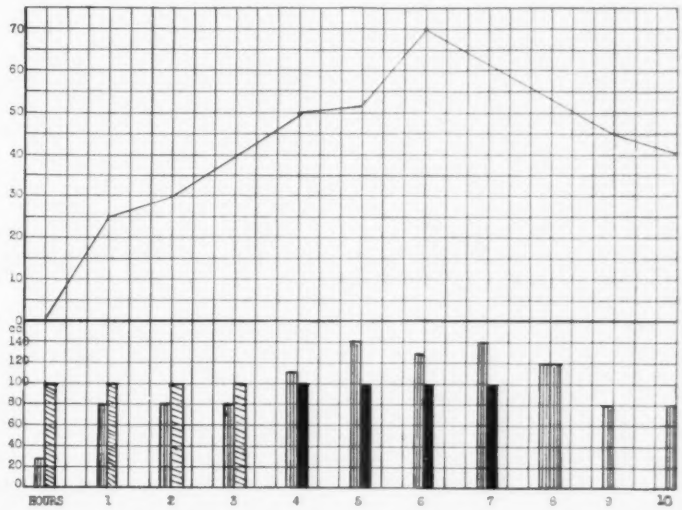

Chart 2.—A comparison of the effect of water with that of 10 per cent beef extract on gastric secretion. The curves represent the free acidity of the gastric contents over a ten hour period.

the administration of beef tea could not be continued indefinitely, and it was found best to vary it considerably, depending on the duration and degree of spontaneous distress. On termination of it, hourly water feeding was usually substituted for the beef tea feeding, followed several days later by the alkali regimen, as may be seen from a study of table 4.

RESULTS

Chart 3 portrays the difference in the rate of complete disappearance of spontaneous pain in the two groups, the average for the first being

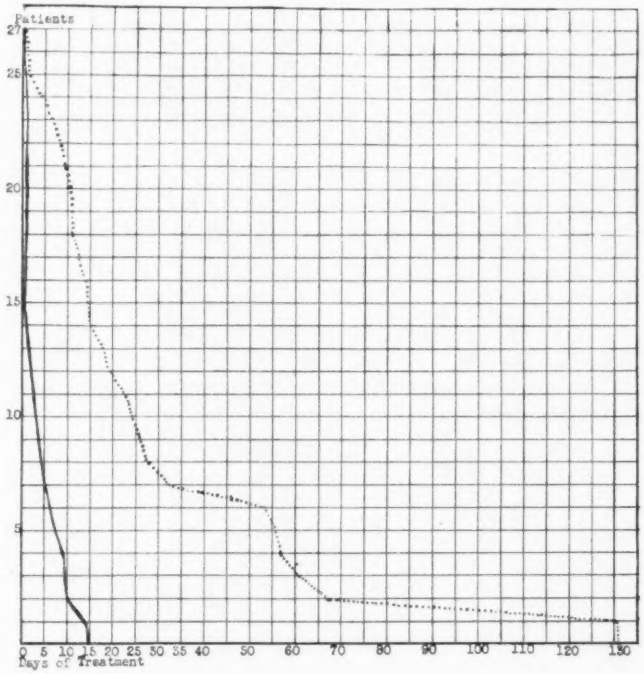

Chart 3.—Curves of the complete disappearance of spontaneous pain. The solid line represents the alkali group (average duration, 2.6 days); the dotted line represents the beef tea group (average duration, 26.6 days).

2.6 days as compared with 26.6 days for the second. It should be stated that most of the spontaneous distress in the alkali group occurred at night, owing apparently to uncontrolled night secretion. It is unusual to have distress from ulcer occur during that portion of the day in which half-hourly feeding of milk and cream and administration of alkali are continued.

TABLE 3.—*"Acid Test" in Alkali Group*

Patient	Kind of Ulcer Shown by Roentgenogram	Duration, Yr.	Duration of Spontaneous Pain Days	Days of Treatment (+ = positive "acid test"; − = negative "acid test")																	Remarks
				1	5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	
1	Duodenal	4.0	0	+	−	−	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
2	Duodenal	5.0	0	+	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Obstruction relieved
3	Gastric	5.0	1	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	..	
4	Duodenal	0.7	0	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	..	High secretion
5	Duodenal	5.0	1	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	
6	Duodenal	4.0	0	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	Slight retention
7	Duodenal	0.5	1	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	Recurrent after acute perforation
8	Duodenal	4.5	0	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	Pulmonary tuberculosis
9	Duodenal	5.0	1	+	−	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	
10	Duodenal	2.0	4	+	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	Obstruction relieved
11	Duodenal	1.5	14	+	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	High secretion
12	Duodenal	10.0	0	+	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	High grade abstruction
13	Duodenal	14.0	7	+	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	High grade obstruction; gastro-enterostomy
14	Duodenal	20.0	0	+	−	+	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	
15	Duodenal	4.0	9	+	+	+	−	−	−	..	..	..	..	..	..	..	..	..	..	..	..	
16	Duodenal	12.0	5	+	+	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	Obstruction relieved
17	Duodenal	18.0	1	+	+	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	
18	Gastric	0.2	1	+	+	+	−	−	−	−	..	..	..	..	..	..	..	..	..	..	..	
19	Gastric	3.0	8	+	+	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	..	Resection
20	Duodenal	6.0	0	+	+	−	+	−	−	..	..	..	..	..	..	..	..	..	..	..	..	
21	Duodenal	2.0	0	+	+	+	+	−	−	−	..	..	..	..	..	..	..	..	..	..	..	
22	Duodenal	0.3	10	+	+	+	+	−	−	−	−	−	..	..	..	..	..	..	..	..	..	Obstruction unrelieved; gastro-enterostomy
23	Multiple gastric and duodenal	13.0	0	+	−	−	−	+	..	..	..	..	..	..	..	..	..	..	..	..	..	Release; previous gastro-enterostomy
24	Duodenal	2.0	3	+	+	+	+	+	−	−	−	..	..	..	..	..	..	..	..	..	..	High secretion
25	Duodenal	10.0	9	+	+	+	+	+	−	−	−	..	..	..	..	..	..	..	..	..	..	Recurrent hemorrhage; high secretion
26	Duodenal	7.0	0	+	+	−	−	+	+	−	−	−	..	..	..	..	..	..	..	..	..	High grade obstruction; gastro-enterostomy
27	Duodenal	6.0	1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	Could not be followed longer
Average.....		6.1	2.8																			Number with obstruction, 8; number operated on, 4

Table 3 presents a summary of the observations on the alkali group, showing not only the results of the "acid tests" but also the duration of ulcer symptoms prior to the patient's entering the hospital, the duration of spontaneous pain and the complications present.

Chart 4 portrays graphically the relationship between the duration of spontaneous pain and the positive "acid test" in the alkali group, the average duration of the former being 2.8 days, whereas that of the latter was 9.7 days. It should not be inferred that the "acid test" character-

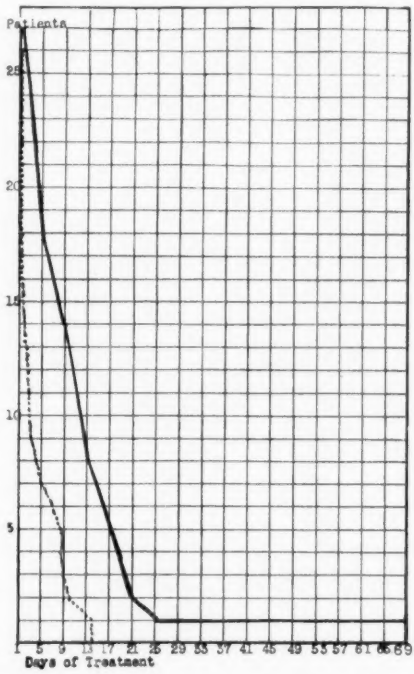

Chart 4.—Relationship of spontaneous pain and positive "acid test" in the alkali group. The dotted line represents persistence of spontaneous pain (average, 2.8 days); the solid line, persistence of positive "acid test" (average, 9.7 days).

istically remains positive for a week after spontaneous distress disappears. It does so usually in cases in which the type of alkali therapy described is employed, which is the "Sippy treatment" modified to conform to the conditions of the experiment, but not in those cases in which the distress disappears spontaneously. Under such conditions, the "acid test" usually becomes negative at about the time the spontaneous distress disappears, as will be noted later in comment on the

TABLE 4.—*"Acid Test" in Beef Tea Group*

Patient	Kind of Ulcer Shown by Roentgenogram	Duration, Yr.	Duration of Spontaneous Pain, Days	Days of Treatment: 1	5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	105	109	114	118	Remarks
1	Duodenal	3.0	0	*B+	W—	P—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
2	Duodenal	12.0	2	B+	—	—	P—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
3	Duodenal	0.2	7	B+	—	—	W—	—	P—	—	—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
4	Duodenal	4.5	8	B+	+	—	—	P—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
5	Duodenal	10.0	2	B+	+	+	—	P—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
6	Duodenal	0.1	13	B+	+	+	—	W—	—	P—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pain on 13th day only, at night
7	Duodenal	8.0	11	B+	+	+	—	—	—	W—	—	P—	—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	High night secretion
8	Duodenal	0.5	9	B+	—	+	+	—	—	P—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
9	Duodenal	15.0	15	B+	+	P+	W+	—	—	—	—	P—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	High grade obstruction; gastro-enterostomy
10	Duodenal	1.5	10	B+	+	+	+	+	—	—	P—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
11	Duodenal	4.0	33	B+	+	+	—	+	—	W—	P—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Slight retention
12	Duodenal	10.0	18	B+	+	+	+	+	—	—	W—	—	P—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
13	Duodenal	0.1	14	B+	+	+	—	A—	R+	P—	—	—	.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Absconded for 6 days between "A" and "R"
14	Duodenal	3.0	23	B+	+	+	+	+	+	—	P—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
15	Duodenal	3.0	16	B+	W+	P+	+	+	+	—	—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	High grade obstruction; partially relieved
16	Duodenal	6.0	24	B+	+	+	W+	+	+	P+	..	.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Release
17	Duodenal	3.5	6	B+	+	+	+	+	+	+	—	P—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
18	Duodenal	5.0	10	B+	+	P+	+	+	+	+	—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
19	Duodenal	11.0	26	B+	+	+	+	+	+	W+	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Absconded; syphilis
20	Duodenal	5.0	27	B+	W+	+	P+	+	+	—	+	—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Slight obstruction
21	Duodenal	0.7	19	B+	—	+	+	+	—	+	P+	+	—	+	—	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Release
22	Duodenal	2.0	53	B+	—	+	+	+	+	—	W—	+	—	+	—	—	—	—	—	P—	—	—	—	—	—	—	—	—	—	—	—	—	—	
23	Duodenal	9.0	56	B+	+	+	+	+	+	W—	+	+	+	P+	+	+	—	—	—	—	—	..	..	..	..	..	..	..	..	..	..	..	..	High grade obstruction
24	Duodenal	5.0	57	B+	+	+	+	—	+	+	+	+	W+	+	+	P+	+	+	—	—	—	—	..	..	..	..	..	..	..	..	..	..	..	High grade obstruction
25	Duodenal	11.0	62	B+	+	+	+	+	+	+	+	+	+	+	W+	P+	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
26	Duodenal	12.0	67	M+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	F+	+	+	—	—	—	—	—	—	—	—	—	—	—	—	Obstruction relieved
27	Duodenal	10.0	131	B+	+	+	+	+	W+	+	—	—	—	—	—	—	+	—	—	—	+	—	—	+	P—	—	—	+	+	—	—	—	—	Hemorrhage; moderate obstruction
Average.....		5.7	26.6																														Number with obstruction, 8; number operated on, 1

* B = 90 cc. beef tea. + = positive "acid test." — = negative "acid test." W = 90 cc. water. P = alkali. A = absconded. R = returned. M = milk and cream only.

beef tea group and as may be seen by a careful study of the data presented. This difference is apparently due to the more prompt relief from distress induced by alkali therapy.

Table 4 summarizes the observations on the beef tea group. Case 15 is of especial interest here. The patient entered the hospital in such severe distress that it was necessary to keep him at absolute rest in bed. During the brief period of the administration of beef tea he continued to have severe pain and finally threatened to leave the hospital unless something was done to give relief. The beef tea was stopped,

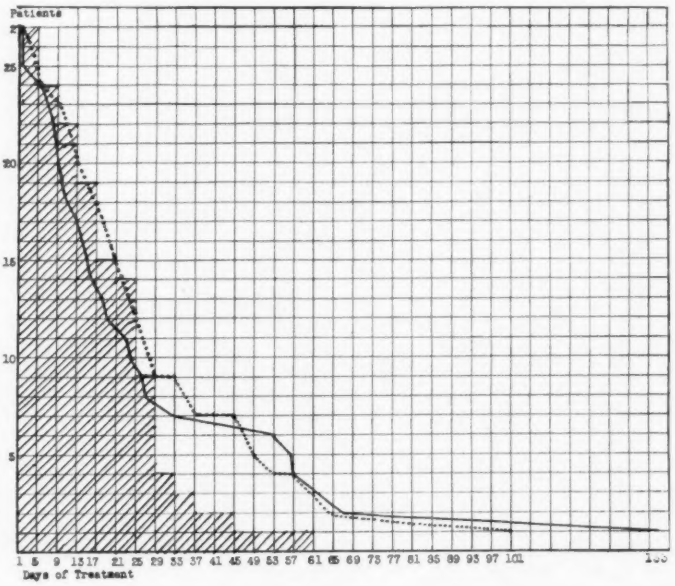

Chart 5.—Relationship of the administration of beef tea to the persistence of pain and the positive "acid test." The dotted line represents persistence of positive acid test (average, 26.9 days); the solid line, persistence of spontaneous distress (average, 26.6 days), and the diagonal lines, the period of administration of beef tea.

water substituted for it, and assurance given that the pain would diminish. It failed to do so, and after another short period the patient again threatened to leave the hospital. Alkalies were then given with the hourly doses of water, as in the regimen of the alkali group. The pain was at once relieved, although it did reappear at intervals during the following week. On the sixteenth day of experimentation and the eighth day of alkali therapy, it disappeared completely. In no other

case was the contrast between the two different forms of therapy so striking.

Chart 5 shows the relationship of the period of the administration of beef tea to the persistence of spontaneous pain and the positive "acid test." In this group, the average duration of spontaneous pain was 26.6 days and that of the positive "acid test" 26.9 days. This would seem to indicate that the cessation of spontaneous pain corresponded

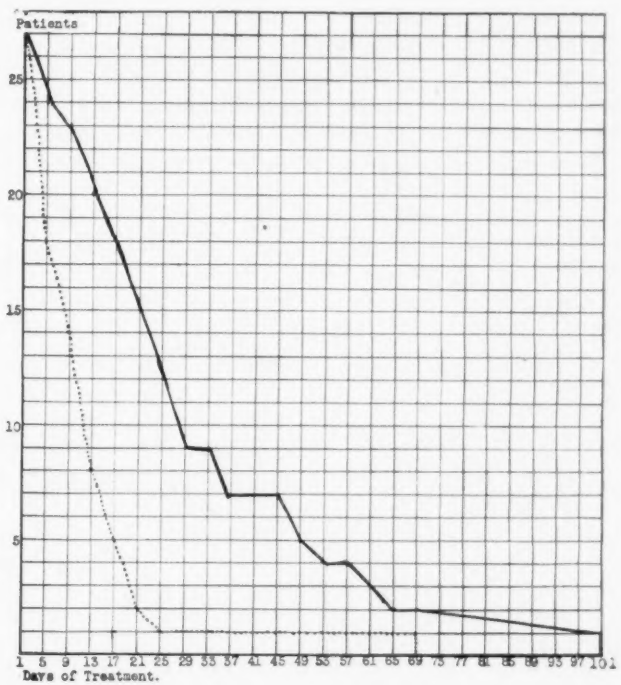

Chart 6.—Persistence of sensitivity to acid test. The dotted line represents the alkali group (average, 9.7 days); the solid line, the beef tea group (average, 26.9 days).

almost exactly with the transition from a positive to a negative "acid test." A study of the curves shows that this was not the case, and a more detailed study of the data presented in chart 6 will disclose further discrepancies. It is significant that in two thirds of this group the spontaneous distress disappeared during the period of administration of beef tea, and the "acid test" became negative before alkali therapy was instituted, while in the other third these changes did not occur until after the alkali therapy had been started.

Chart 6 gives a comparison of the rates of transition from a positive to a negative "acid test" in the two groups, the average length of time required for the alkali group being 9.7 days as compared with 26.9 days for the beef tea group.

A final summary of the experiments is given in table 5, which needs little additional comment. The method of selecting the cases has been described. The average duration of symptoms in one group is comparable with that in the other; the number of cases judged clinically to be complicated by more or less obstruction happened to be the same in each group; the numbers referred later for surgical intervention differed, but this fact has no bearing on the experiment, for the decision rested on entirely irrelevant considerations; the average duration of spontaneous and of induced distress was definitely less in the alkali group; the average quantity of free acidity of the gastric content

TABLE 5.—*Comparison of Alkali and Beef Tea Groups*

Points of Comparison	Alkali	Beef Tea
Number of gastric ulcers	4	0
Number of duodenal ulcers	23	27
Total	27	27
Average duration of ulcers in years	6.1	5.7
Number complicated by pyloric obstruction	8	8
Number later referred for operation	4	1
Average duration of spontaneous pain—days	2.8	26.6
Average duration of sensitivity to acid test—days	9.7	26.9
9:00 p. m. aspiration—average quantity, cc	80.5	156.8
		Water 195.0
		Alkali 103.0
Average free acidity	13.0	28.8
		Water 30.7
		Alkali 17.0

obtained at 9 p. m. was much less in the first series than in the second. Apparently, the stomach emptied more rapidly under the alkali therapy than under the other regimens. It is difficult to know how much importance to attach to this fact, but when one considers that there was probably considerable gastric content present continuously in both groups from 7 a. m. to 7 p. m., an average difference of perhaps 80 cc. seems of questionable significance.

COMMENT

In many respects, the most significant result in these experiments is that two thirds of the patients in group 2 became free from spontaneous distress during the period of administration of beef tea and acid-insensitive without alkali therapy, indicating thereby desensitizition of the pain-producing mechanism. This was to have been expected, of course, from the fact that the majority of ulcers become symptom-free and presumably acid-sensitive without any particular treatment. Any form of therapy usually suffices to bring about a period of remission.

This desensitization of the pain-producing mechanism, whether spontaneous or induced, apparently indicates that some progress has been made by the reparative processes in the ulcer. Stimulation of gastric secretion by means of the hourly feeding of beef tea did not stop them; it did not stop the natural tendency of the ulcer to heal spontaneously. This constitutes further evidence that, regardless of what the etiology of ulcer may be, and regardless of the cause of chronicity, the natural and usually the dominating tendency in any given ulcer is toward healing.

The next most significant observation is that neutralization of the gastric free acidity by means of alkalis definitely increased the rate of desensitization of the pain-producing mechanism. There is reason to think that some correlation exists between this and the healing process, that desensitization signifies some progress toward healing. The conclusion seems reasonable, therefore, that neutralization of the gastric free acidity favors healing. This may be due to protection of the ulcer surface from the destructive action of hydrochloric acid, to decreased gastric emptying time, as Dragstedt [10] suggested in his experimental work, to diminished spasm or perhaps to other unknown factors. But regardless of what the explanation may be, healing apparently proceeded at a faster rate in the alkali group.

SUMMARY

1. Desensitization of the pain-producing mechanism occurred in both groups of patients.

2. The duration of the positive "acid test" exceeded the duration of spontaneous pain definitely in the alkali group, but only slightly in the beef tea group.

3. Stimulation of gastric secretion by the hourly administration of beef tea did not stop the healing process.

4. Attempted neutralization of the gastric free acidity definitely favored the healing process, as was indicated by the more rapid disappearance of spontaneous pain and the more rapid transition from a positive "acid test" to a negative "acid test."

10. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

LABORATORY STUDIES IN EPILEPSY*

JOSEPH FELSEN, M.D.
NEW YORK

The data in these papers represent a continuation of the work published in 1924,[1] including a follow-up study over a period of from five to six years. Some of the patients originally studied were dropped because they had discontinued hospitalization, and others were substituted. Table 1 therefore serves to reconcile the old and new numbers, each number always indicating the same patient.

The general plan of study was to investigate by laboratory and clinical methods the various body systems (e. g., circulatory, digestive, ductless glandular, etc.), to draw tentative conclusions in regard to each system and finally to correlate the observations. A review of the literature was made after this work was completed. The cooperation of a specially trained nursing staff and the use of a locked ward and mimeographed forms for the accurate recording of observations were indispensable for the completion of these studies as they now stand.

Nearly all of the patients studied fell in the age group from 21 to 31 years, all being men. Wherever possible, normal controls of approximately the same age were secured from among patients who had no ascertainable disability or who were receiving physical therapy for healed wounds of the extremities.

THE BLOOD

THE FORMED BLOOD ELEMENTS, INTERPAROXYSMAL PERIOD

Interparoxysmal observations were made on the blood of fifty-seven epileptic persons. In each case, the blood was taken during a tranquil period, from twenty-four to seventy-two hours after the last seizure and not immediately preceding a subsequent one. Of course, one could not always be sure of petit mal attacks.

Platelet Count.—For the platelet count the method used was that of Wright and Kinnicutt. The average platelet count of healthy adults is from 300,000 to 350,000 per cubic millimeter. Five patients, all of whom showed a tendency to cutaneous petechial spotting during an attack, were studied. Two of these counts were distinctly low: 200,000 (no. 16); 103,760 (no. 65). No. 65 also had a prolonged coagulation time (nine minutes).

* Submitted for publication, Jan. 23, 1930.

1. Felsen, Joseph: Laboratory Studies in Epilepsy: I. Fractional Gastric Analysis, Arch. Int. Med. **34**:147 (Aug.) 1924.

Coagulation Time.—In the determination of the coagulation time, the gross test tube method of Lee and White was used. The accepted norm is from six to seven minutes. Of thirty-four patients, ten showed a lengthened coagulation time of eight minutes or more (nos. 2, 5, 19, 20, 21, 28, 49, 52, 61 and 65).

Bleeding Time.—Duke's method was used in the determination of the bleeding time, the upper limit of the norm being from two to three minutes. Of twenty-two patients examined, none exceeded this time, including the two having low platelet counts.

Fragility Test.—The fragility tests were made according to the method of Griffin and Sanford. Normally, hemolysis begins in a saline concentration of about 0.425 per cent and is complete in 0.35 per cent. Some authors place the lower limit at 0.32 per cent. Of the twenty-four estimations in this series, only one was worthy of note (from 0.405 to

TABLE 1.—*Key to Numbering of Epileptic Patients Studied in Old and New Groups* *

Old Number	Present Number	Old Number	Present Number	Old Number	Present Number	Old Number	Present Number
26	1	19	19	16	32	17	57
25	3	45	20	15	35	18	58
52	6	24	21	55	40	41	59
36	7	9	24	14	44	5	60
28-29	8	10-11-12	25	42	45	50	62
27	9	56	26	48	49	20-21	65
2	11	33	27	13	50	23	67
47	12	34	28	32	51	22	68
35	15	37	29	6	52	43	70
49	17	7	31				

* Thirty-eight patients of the original group remained for the subsequent studies; thirty-five other patients were substituted.

0.155). This fragility occurred in the patient (no. 65) having a low platelet count (103,760) and a prolonged coagulation time (nine minutes). There was a distinct tendency to petechial hemorrhages into the skin and conjunctivae.

Hemoglobin.—The hemoglobin content was measured by the Dare instrument checked against a prepared Sahli test. Of the forty-four patients examined, none showed any evidence of hemoglobinemia. Each had 85 per cent or above.

Erythrocyte Count.—The number of erythrocytes was estimated by means of the Levy counting chamber with Neubauer ruling, certified. Pipets were checked against the certified standard type. The dilution was 1 to 200. One hundred $\frac{1}{400}$ mm. areas were counted in duplicate. Of fifty-six estimations, nearly all averaged about 4,000,000 cells per cubic millimeter, indicating no marked cytanemia. None fell below 3,600,000.

Leukocyte Count.—Leukocytes were counted by the same method as the erythrocytes, except for a dilution of 1 to 20. Of fifty-six patients

examined, three (nos. 22, 46 and 54) showed a moderate leukocytosis not accounted for by any ascertainable existing infection. Eight showed a leukopenia of 6,000 or less (nos. 16, 19, 34, 37, 48, 53, 68 and 70).

Differential Blood Picture.—The differential blood picture was obtained by Wright's method. Of fifty-six patients studied, eleven (nos. 1, 6, 17, 20, 27, 28, 32, 39, 44, 49 and 50) showed a lymphocyte count of 31 per cent or over, one of them presenting a count as high as 52 per cent. In this latter case, the neutrophils amounted to 46 per cent. In all there were seven patients with neutrophilic counts of 60 per cent or less. The only other unusual observation was four instances of transitional cells amounting to 5 per cent or over.

Summary.—The interparoxysmal blood picture of fifty-seven epileptic patients may be summarized as follows:

1. Low platelet count: Two (of five selected patients) showed a low platelet count.

2. Prolonged coagulation time: Ten (of thirty-four patients) had a prolonged coagulation time. One of these also had a low platelet count.

3. Fragility test: One (of twenty-four patients) gave evidence of increased resistance of the blood to saline solution. This occurred in the patient having a prolonged coagulation time and a low platelet count.

4. Leukocytes: Three (of fifty-six) showed leukocytosis. Eight (of fifty-six) showed leukopenia.

5. Differential blood picture: Eleven (of fifty-six) showed moderate lymphocytosis. In four, there was an increase in transitional cells.

Review of the Literature.—Table 2 shows the essential results obtained by five other observers.

Patterson's [2] studies were apparently limited to distinct endocrine types. Some variations in the reported figures can probably be accounted for by the method used. Thus, Spangler [3] used the Boggs instrument for obtaining the coagulation time.

There seems to be considerable difference in the reports on the total leukocyte count. This may be due to the time the specimen was taken, i. e., its proximity to an impending seizure or to a meal, or it may be due to some factor independent of the epilepsy (e. g., infection).

THE FORMED BLOOD ELEMENTS, PAROXYSMAL PERIOD

Observations were made on specimens of blood taken in each instance during a paroxysm or immediately on the cessation of the violent clonic movements. Complete examinations could be made in only a few cases.

2. Patterson, H. A.: Haematological Pictures in Endocrine Syndromes, Am. J. Psychiat. **2**:427, 1922-1923.

3. Spangler, R. H.: Blood Findings in Epilepsy, Lancet **1**:910, 1916.

Coagulation Time.—Normal coagulation time was shown by eight patients. Of these, two (nos. 61 and 65) had shown a lengthened coagulation time in the interparoxysmal period.

Fragility Test.—Normal fragility was found in seven cases and not essentially different from that observed during the interparoxysmal period.

Erythrocyte Count.—The erythrocyte counts on twelve patients were approximately the same as in the interparoxysmal period, except that of one patient (no. 65). In this instance, the lapse of ten months made comparison of the figures of the second seizure difficult.

TABLE 2.—*Comparison of the Observations on the Blood in Epilepsy (Interparoxysmal Period) Recorded in the Literature*

Author	Cases	Platelet Count	Coagulation Time	Bleeding Time	Fragility Test	Hemoglobin, %	Red Blood Cells	White Blood Cells	Small Lymphocytes	Eosinophils
Onuf	19	.....	.....	.....	.....	106	4,895,000 to 5,405,000	7,802	.....	.....
Spangler	369	.....	1.5 to 4.75 min. in 98 cases	.....	.....	84 in 100 cases	Normal	Normal	Normal	Normal
Craig Colony	...	.....	.....	.....	.....	.....	.....	10,800 to 34,200	.....	.....
Patterson	128	.....	.....	.....	.....	.....	.....	Leukocytosis	.....	.....
Smith	...	.....	.....	.....	.....	50-75	4,520,000	.....	.....	.....
Felsen	57	Low in 2 of 5 selected cases	Prolonged in 10 of 34 cases	Normal	Increased resistance in 1 of 34 cases	Normal	Normal	3 of 56 leukocytosis; 8 of 56 leukopenia	11 of 56 increased	Normal

Leukocyte Count.—Of twelve patients, eight showed leukocytosis (nos. 9, 13, 31, 57, 61, 63, 64 and 65), two having counts of 17,800 (no. 13) and 18,400 (no. 65). It is interesting to note that the latter had shown a somewhat lower figure (12,200) during a seizure ten months previously.

Differential Blood Picture.—Eleven patients (nos. 4, 9, 13, 31, 56, 57, 58, 61, 63, 64 and 65) showed a lymphocytic preponderance of 31 per cent or over (three having counts of 50 per cent or above). All of them, except one (no. 61), had shown normal figures in the interparoxysmal period.

Summary.—Blood taken during paroxysm in a series of twelve epileptic patients showed essentially leukocytosis and lymphocytosis.

Review of the Literature.—Spangler [3] stated that while the total leukocyte count during the interparoxysmal period is normal there is a leukocytosis at the time of and for twenty-four hours following a seizure.

He also stated that the coagulation time is shortened in the interparoxysmal period. Turner [4] reported a similar observation during a seizure but a prolonged coagulation time following the fit. Others noted a marked prolongation of the coagulation time due to a diminution in the quantity of fibrin ferment just before a fit.

Féré [5] noted a relative increase in the number of erythrocytes, due to the loss of fluid during an attack (secretions, sweat). Many of the cells diminish in size. There is also a destruction of hemoglobin and an increase in the number of platelets.

Pugh [6] found a decrease in the number of leukocytes, beginning a few hours before a fit and often continuing up to the paroxysm. He also stated that during the fit the leukocyte count is high, and that it attains its maximum from fifty to seventy minutes after cessation of the fit. The

TABLE 3.—*Comparison of the Observations on the Blood in Epilepsy (Paroxysmal Period) Recorded in the Literature*

Author	Coagulation Time	Red Blood Cells	White Blood Cells	Lymphocytes	Remarks
Turner	Shortened	.....	Increased	.....	Coagulation time prolonged after fit
Féré	.....	Increased	.....	.....	
Pugh	.....	.....	Increased	Increased	Decrease in white blood cells just before fit
Onuf	.....	.....	Increased	.....	
Spangler	.....	.....	Increased	.....	
Wuth	.....	.....	Increased	Decreased	Eosinophilia after convulsion
Felsen	Normal	Normal	Increased	Increased	

increase is in the number of lymphocytes. There is also an increase in the number of eosinophils from two to ten hours after a seizure.

Onuf and Lograsso,[7] studying two patients intensively at a definite time each day, found leukocytosis just before the fit and for many hours after its cessation. The extent of the rise is apparently inconstant and exists partly independent of seizures.

Wuth [8] summarized the work on leukocytic reactions in relation to epileptic convulsions as set forth in table 4.

4. Turner, J.: Some Further Observations Bearing on the Supposed Thrombotic Origin of Epileptic Fits, J. Ment. Sc. **54**:638, 1908.

5. Féré, C.: Note sur l'altérabilité des globules rouges et sur la présence temporaire d'un grand nombre de globulins dans le sang des épileptiques après les accès, Compt. rend. Soc. de biol. **1**:213, 1889.

6. Pugh, R.: On Certain Blood Changes in Idiopathic Epilepsy, Brain **25**: 501, 1902.

7. Onuf, B., and Lograsso, H.: Researches on the Blood of Epileptics, Am. J. M. Sc. **131**:269, 1906.

8. Wuth, C.: Blood Changes in Convulsions Especially in Epilepsy, Bull. Johns Hopkins Hosp. **38**:389, 1926.

Comment.—It appears difficult to reconcile these contradictory observations. It seems that a control observation of the blood picture during a period of freedom from disease is necessary for the accurate interpretation of a patient's blood picture in the epileptic state. Not infrequently a normal leukocyte but a high lymphocyte count is found for healthy adults. The frequent occurrence of a similar picture in children is well known. Moreover, in this series care was taken to rule out variations from the normal due to coexisting disease (e. g., diseases of the skin, asthma, influenza). A leukocytosis with a relative lymphocytosis occurs with unusual frequency during an epileptic paroxysm. This is probably not due to concentration of the blood, since the erythrocyte count remains approximately normal, the control being the blood picture of the same patient in the interparoxysmal period.

TABLE 4.—*Comparison of Observations on the Blood in Relation to the Seizure (Wuth)*

Before Seizure	During Seizure	After Seizure
Leukocytosis (Riebes)	Leukocytosis (Goedicke)	Leukocytosis (Itten, Riebes, Schultz)
Leukopenia (Hartman, Di Gaspero)	Lymphopenia (Di Gaspero)	Lymphocytosis (Riebes)
Lymphocytosis (Schultz, Itten, Zimmermann, Gorrieri)	Lymphocytosis (Zimmermann, Schultz, Rhode)	Eosinophilia (Gorrieri, Di Gaspero, Schultz)
Eosinophilia (Gorrieri)	Eosinophilia (Zimmermann, Schultz)	

CHEMISTRY OF THE BLOOD, INTERPAROXYSMAL PERIOD

Examinations were made of the blood chemistry of fifty-five epileptic patients during the interparoxysmal period. All specimens were taken after an all night fast (usually fourteen hours). The Folin-Wu system of analysis was used for dextrose, urea, nonprotein nitrogen, uric acid and creatinine; Whitehorn's method for chlorides, and Levy, Rowntree and Marriott's method for p_H values. As regards the latter, Marrack and Thacker [9] found that the error of the calorimetric method does not exceed 0.05 with normal plasma nor 0.12 with abnormal plasma. Variations occur due to temperature, venosity of the blood and hyperpnea. The Clark-Collip modification of the Kramer-Tisdall method was used for calcium and Hammerschlag's method for specific gravity.

Dextrose.—Of fifty patients, eight (nos. 9, 10, 13, 28, 44, 45, 49 and 63) had 75 mg. or less of dextrose per hundred cubic centimeters of blood, i. e., were distinctly hypoglycemic. One of them was markedly

9. Marrack, J., and Thacker, G.: The Reaction of the Blood in Epilepsy, Brit. J. Exper. Path. **7**:265, 1926.

so (no. 63), and the value had no definite relation to a preceding or subsequent fit. Six patients were hyperglycemic (nos. 21, 24, 37, 40, 58 and 65), having 120 mg. or over per hundred cubic centimeters, and apparently this was not due to an existing diabetes or postprandial effect.

Urea Nitrogen and Nonprotein Nitrogen.—In fifty-five patients, urea nitrogen and nonprotein nitrogen were well within normal limits (from 14 to 20 mg. for the former and from 20 to 40 mg. for the latter).

Uric Acid.—The normal limits for uric acid are from 2 to 3 mg. Eight of forty-one patients had over 3 mg. (nos. 2, 5, 21, 24, 25, 34, 36 and 37), the uric acid in the blood of two (nos. 34 and 36) reaching as high as 4.01 and 5.23 mg., respectively.

Creatinine.—No essential deviations from the norm (from 1 to 2 mg.) were encountered (fifty-one patients).

Chlorides (as NaCl).—Of fifty-five patients, thirty-six (nos. 3, 4, 6, 8, 9, 10, 11, 12, 17, 20, 21, 24, 25, 26, 28, 29, 31, 32, 34, 37, 39, 40, 44, 45, 52, 55, 57, 58, 60, 61, 62, 63, 68, 69, 70 and 71) had 600 mg. or over. Figures of 800 (no. 69) and 850 (no. 62) were encountered, the former amount being found in the blood of a patient with epilepsy of moderate severity, the latter in that of a patient who at operation was relieved of a large intracranial endothelioma. Most of these figures can be accounted for by the salt-loving tendencies of these patients. This was proved by the necessity of placing those on a salt-poor diet under the most careful supervision, as they often spoiled three or four days' analyses by their surreptitious acquisition of salt.

Hydrogen Ion.—No abnormal concentrations of hydrogen ions were noted in nineteen examinations (p_H of from 7.6 to 7.8).

Calcium.—Sixteen patients showed no deviation from the norm (from 7 to 10 mg.) in respect to calcium.

Specific Gravity.—Twenty-four estimations of specific gravity ranged from 1.065 to 1.071 well within the normal limits (from 1.045 to 1.075).

Review of the Literature.—Table 5 summarizes the observations of various investigators in regard to the blood chemistry during a quiescent period. Dufour's[10] case was that of a young woman who became epileptic after several injections of neoarsphenamine. The urea concentration of the quiescent blood was from 25 to 40 mg. per hundred cubic centimeters; the concentration rose a few hours before a seizure to 84, dropping to nearly the former figure by the next day.

Of variations in the chemical constituents of the blood of the epileptic patient examined during the quiescent period, the two most fre-

10. Dufour, H., and Semelaigne, G.: Sur un trouble humoral passager, précédent la crise d'épilepsie; variation de l'urée sanguine, Bull. Soc. méd. d. hôp. de Paris **44**:58, 1920; abstr., J. A. M. A. **74**:985 (April 13) 1920.

quently encountered by various investigators were those of dextrose and calcium. That these variations are not specific for essential epilepsy is apparent from the divergent opinions of many. I have been unable to verify the low calcium content and am convinced that all of the variations exist apart from any direct relationship to the pathologic condition known as "epilepsy." To be regarded as significant, they must occur with much greater constancy.

Reports on other constituents of the blood have been made. Thus, Hamilton [11] studied the bicarbonate, inorganic phosphorus and total

TABLE 5.—*Comparison of Observations on the Blood Chemistry in Epilepsy (Interparoxysmal Period) Recorded in the Literature*

Author	Dextrose	Urea N	Nonprotein	Uric Acid	Creatinine	Chloride	p_H	Calcium	Specific Gravity	Cases
Daly	Normal	.....	.....	.....	.....	.....	.....	.....	.....	1
Dufour	.....	25 to 40 mg.	.....	.....	.....	.....	.....	.....	.....	1
Boutter	.....	.....	.....	.....	.....	.....	.....	.....	.....	11
Lennox	.....	Normal	Normal	Normal	Normal	.....	.....	.....	.....	129*
Sherrill	Normal	High	.....	.....	.....	Normal	.....	.....	.....	6
Hamilton	.....	.....	.....	.....	.....	Normal	.....	Normal	.....	17
Marrack	.....	.....	.....	.....	.....	.....	7.3 to 7.5	.....	.....	—
Cullen, Bigwood, Myers	.....	.....	.....	.....	.....	.....	Low 7.3 to 7.43	.....	.....	—
Prior	.....	.....	.....	.....	.....	.....	.....	Diminished	.....	35
Bigwood	.....	.....	.....	.....	.....	.....	.....	Diminished	.....	35
Pezzali	Normal	.....	Normal	.....	.....	Normal	.....	.....	.....	5
Felsen	Of 50, 8 hypoglycemia; 6 hyperglycemia	Normal (55 patients)	Normal (55 patients)	Of 41, 8 high	Normal (51 patients)	Of 55, 36 high	Normal (19 patients)	Normal (16 patients)	Normal (24 patients)	As stated

* Amino-acid normal.

fixed base in the blood of seventeen epileptic patients and found the amounts to be normal (HCO_3, from 55 to 70 per cent by volume; P, from 2.6 to 6 mg.; total base, from 153 to 161 cc. 0.1 N). Spangler,[7] examining twenty-one epileptic patients and three controls, found a lowered alkalinity of the blood (186 mg. as compared with the norm of 266 mg. of sodium hydroxide to a hundred cubic centimeters of blood). A similar result was obtained by Pugh,[12] and Dautrebande [13] described an

11. Hamilton, B.: A Comparison of the Concentration of Inorganic Substances in Serum and Spinal Fluid, J. Biol. Chem. **65**:101, 1925.

12. Pugh, R.: The Alkalinity of the Blood in Mental Diseases, J. Ment. Sc. **49**:71, 1903.

13. Dautrebande, L.: Acid-Base Balance of the Blood in Epilepsy, Compt. rend. Soc. de biol. **94**:133, 1926; abstr., J. A. M. A. **86**:1323 (April 24) 1926.

alkaline substance which has no affinity for carbon dioxide in vivo, as was previously reported by Bisgaard, Tarlow and Norvig. Bigwood [14] regarded epilepsy as a disturbance of the body's neutralizing mechanism (an alkalosis). This involves especially a concentration of blood plasma in calcium ions—an essential factor in the regulation of cellular excitability in general. In a study of thirty-five epileptic patients, he [15] found that attacks occurred only if the alkalosis was accompanied by a low blood calcium. Claude [16] and his co-workers, on the other hand, reported that induced alkalosis in dogs with epileptigenous lesions does not provoke epileptic seizures unless a toxic factor is present in addition.

Popea and Vicol [17] found a diminution in the cholesterol content of the blood of sixteen epileptic patients suffering from frequent seizures.

Luck and his co-workers [18] found the ammonia content raised in the blood of three of four epileptic patients after a seizure (the norm being 0.10 mg. per hundred cubic centimeters). They did not regard this of etiologic importance as an increased blood ammonia also occurs during starvation—a method often used to lessen the frequency of convulsions. They explained the uniformly high ammonia figures of Bisgaard and Norvig [19] as being due to the method used.

Comment.—In the present series there appear to be no significant changes in the blood dextrose, urea nitrogen, nonprotein nitrogen, uric acid, creatinine, sodium chloride, hydrogen ion concentration, calcium or specific gravity. Almost all of the deviations from the norm checked at a subsequent examination one week later, after seven days of salt-poor diet, had returned to the average level. After comparison of these figures with those in the average run of cases in the same hospital, it seems that similar variations are encountered in nonepileptic groups, including patients without any ascertainable disability.

---

14. Bigwood, E. J.: L'équilibre physico-chemique du sang dans l'épilepsie, J. de physiol. et de path. gén. **22**:70 and 94, 1924.

15. Bigwood, E. J.: Blood Calcium Deficiency in Epilepsy, Compt. rend. Soc. de biol. **90**:98, 1924; abstr., J. A. M. A. **82**:926 (March 15) 1924.

16. Claude, H.; Rafflin, R., and Montassut, M.: Rôle of Alkalosis in Epileptic Seizures, Compt. rend. Soc. de biol. **94**:1334, 1926; abstr., J. A. M. A. **87**:1160 (Oct. 2) 1926.

17. Popea and Vicol: Cholesterolemia in Epileptic Seizures, Compt. rend. Soc. de biol. **93**:749, 1925; abstr., J. A. M. A. **85**:1518 (Nov. 7) 1925.

18. Luck, M. J.; Thacker, G., and Marrack, J.: Ammonia in the Blood of Epileptics, Brit. J. Exper. Path. **6**:276, 1925.

19. Bisgaard, A., and Norvig, J.: Causation and Treatment of Epilepsy, Hospitalstid. **63**:49, 1920. Norvig, J.: Metabolic Anomalies in Psychoses, Acta med. Scandinav. **60**:211, 1924.

CHEMISTRY OF THE BLOOD, PAROXYSMAL PERIOD

The figures in table 6 represent the results of examinations of blood specimens taken from eleven patients, in each case immediately after the cessation of a paroxysm. The proximity of the epileptic ward nearly always enabled a technician to reach the patient before the seizure was over. Only single seizures are included. This was done in order to obtain some degree of uniformity, as the results obtained after single and those obtained after multiple seizures are not comparable.

Dextrose.—Three patients had a hypoglycemia below 60 mg. (nos. 13, 24 and 67). On one previous examination (interparoxysmal), patients 13 and 67 had low figures. Patient 24 was alternately high and low at two previous tests during a quiescent period. Of the remaining eight patients, nearly all showed a lower concentration of dextrose than on two other occasions.

TABLE 6.—*Chemistry of the Blood During the Paroxysmal Period (Eleven Epileptic Patients)*

Patient	Dextrose*	Urea Nitrogen	Non-protein Nitrogen	Uric Acid	Creatinine	Sodium Chloride	Hydrogen Ion	Calcium	Specific Gravity
4	90.0	14.3	38.0	....	....	663.0	7.8	...	.....
9	100.0	14.2	21.9	1.15	1.01	676.5	...	...	.....
13	58.9	12.8	31.0	....	0.91	.....	...	...	.....
24	52.9	17.6	24.2	....	....	.....	...	...	.....
25	118.0	15.0	28.0	2.50	0.86	490.0	...	...	.....
37	106.3	15.2	30.0	....	1.36	610.0	...	...	.....
57	117.6	12.2	12.8	....	1.87	673.0	7.6	8.4	1.004
61	90.0	19.0	31.5	....	1.50	693.0	...	...	.....
65	108.0	11.5	36.0	....	....	656.0	7.5	...	1.070
67	56.9	15.2	31.5	....	1.47	620.0	...	...	.....
72	90.0	12.0	22.0	2.00	0.70	580.0	...	...	.....

* Values throughout the table in milligrams per hundred cubic centimeters.

Other Observations.—The other chemical constituents were within normal limits. The work on the blood chemistry is rather fragmentary, because the patient would often leave the hospital before all of his examinations were complete and therefore no controls were to be had, i. e., during the quiescent period. These patients are not included in the studies.

Review of the Literature.—Table 7 summarizes the observations of other investigators on the chemistry of the blood immediately after a seizure. Chemical constituents other than those studied in my series have been studied in relation to seizures. Thus, Wuth [8] reported an increase in the serum protein. In one case, Hamilton [11] found normal values for bicarbonate, phosphorus, total base, calcium and sodium chloride. Pugh [12] reported a diminution in the alkalinity of the blood both before and after a fit. Pezzali,[20] studying five epileptic patients,

20. Pezzali, G.: The Blood in Epilepsy, Riforma med. **39**:433, 1923; abstr., J. A. M. A. **81**:341 (July 28) 1923.

noted a decrease in cholesterol and an increase in calcium during seizure. Hypocholesterolemia was also reported by Popea and Vicol [17] to have occurred in sixteen epileptic patients. Luck and his co-workers [18] found an increase in the blood ammonia in three of four patients.

Comment.—Chemical examination of the blood of eleven epileptic patients immediately after seizure showed no changes other than those which might reasonably be ascribed to physical exertion.

EFFECT OF SALT-POOR DIET ON CHEMISTRY OF THE BLOOD

It was noticed in the course of some studies on the daily habits of epileptic persons that many of those with a most severe type of the disease had a voracious appetite for salt. This tendency did not appear to be present in a similar control group of nonepileptic persons. As an

TABLE 7.—*Comparison of Observations on the Blood Chemistry in Epilepsy (Paroxysmal Period) Recorded in the Literature*

Author	Dextrose	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	Chlorides	Hydrogen Ion	Cases
Daly	Normal with tendency to low values	.....	.....	.....	.....	.....	.....	4
Boutter	.....	Normal	.....	.....	.....	.....	.....	11
Lennox	.....	Normal	Normal	Normal	Normal	.....	.....	1
Krainsky, Rhode, Allers	.....	.....	Increased	.....	.....	.....	.....	..
Wuth	.....	.....	Increased (1 case)	Increased (1 case)	Increased (1 case)	.....	.....	5
Pezzali	.....	.....	Normal	.....	.....	Normal	.....	5
Felsen	Tendency to low values	Normal	Normal	Normal	Normal	Normal	Normal	11

illustration of this point, it was found that many patients exceeded the average daily requirement of 3 or 4 Gm. by from 40 to 60 Gm. With a view to noting the effects of an almost complete withdrawal of sodium chloride from the diet, a separate table and feeding hour were established for small groups. The distress caused by this measure necessitated the closest scrutiny and the use of a locked ward in most cases could not be prolonged beyond one week. The salt-poor diet of Friedenberg was used.

Dextrose.—Six patients showed some increase in dextrose, i. e., over 120 mg. per hundred cubic centimeters (nos. 8, 21, 22, 62, 65 and 68). Of these, two (nos. 21 and 65) had previously shown mild hyperglycemia. Hypoglycemia, i. e., below 80 mg., was observed in four patients (nos. 29, 44, 57 and 60). Of these, one (no. 44) had previously shown a low figure.

Urea Nitrogen.—No unusual values of urea nitrogen were noted.

Nonprotein Nitrogen.—No unusual values of nonprotein nitrogen were noted.

Uric Acid.—Ten patients (nos. 11, 21, 34, 36, 39, 51, 62, 68, 69 and 71) had a blood uric acid content of over 3 mg. Of these, two (nos. 68 and 69) showed 6.25 and 7.3 mg., respectively; three (nos. 21, 34 and 36) had previously shown high figures. Several patients had unusually low blood uric acid, probably accompaning the increased elimination of fluid through the kidneys which regularly follows the use of a salt-poor diet.

Creatinine.—No changes in the creatinine values were worthy of note.

Chlorides (as NaCl).—After six days of almost total deprivation of sodium chloride, seventeen (nos. 3, 4, 5, 8, 10, 21, 34, 39, 40, 44, 48, 55, 57, 58, 61, 70 and 71) of forty-one patients still had a blood chloride content of over 600 mg.—41 per cent, as compared with 65 per cent with high figures before the salt-poor diet was instituted. Of the seventeen, all but two (nos. 5 and 48) had previously had high figures. On the whole, the general tendency was toward a definite, marked reduction in the chloride level, this level in two patients (nos. 29 and 51) reaching 330 and 350 mg., respectively.

Calcium.—No changes were found in the calcium content.

Specific Gravity.—The specific gravity showed no changes.

Review of the Literature.—Sherrill [21] subjected four epileptic patients to a salt-free diet for ten weeks. The plasma chloride was considerably reduced, the most marked reductions occurring in the patients with higher figures at the outset, who also showed greater elimination in the urine. The urea, originally high, was reduced somewhat, and the blood sugar was unaffected. No therapeutic benefit was obtained.

Comment.—There appears to be no evidence that a salt-poor diet used for a period of six days has any effect on the blood chemistry other than reduction of the chloride content. This may be of importance, however, in connection with epileptic seizures associated with renal disturbance, and will be discussed later.

THE WASSERMANN REACTION OF THE BLOOD

The Wassermann test was performed on the blood of seventy-three epileptic patients. The technic employed involved the use of plain and cholesterolized antigens and the human hemolytic system. Inactivation was for fifteen minutes at 56 C., and incubation was at 37.6 C. Multiple positive and negative serums and antigenic, hemolytic and corpuscle

21. Sherrill, J. W.: Metabolic Observations in Psychiatric Cases, J. Metab. Research **5**:129, 1924.

controls were used each day. Readings were made at once and after overnight retention in the icebox.

Observations.—Of seventy-three patients, two (nos. 16 and 41) were found to have positive reactions. One other (no. 72) exhibited an unusual phenomenon. On Dec. 3, 1921, the Wassermann reaction of the blood was negative. On July 12, 1922, just after a seizure, blood withdrawn gave a positive (4+) reaction, as also on July 17. By July 19, the reaction was negative and remained so. This patient was under observation and underwent frequent physical examinations during the entire period and had not apparently contracted syphilis.

Comment.—Attention is called to the unusual effect of a seizure on the Wassermann reaction in one case. The only other explanations are: (1) an error in technic and (2) infection subsequent to the first test with spontaneous subsidence of virulence. The frequency with which the blood was tested and the ultimate return to negativity probably rule out both of these.

RENAL FUNCTION

PHENOLSULPHONPHTHALEIN EXCRETION

In the determination of phenolsulphonphthalein excretion, the method of Rowntree and Geraghty was used. The patient empties the bladder without the use of a catheter. He then drinks two glasses (approximately 500 cc.) of water. Phenolsulphonphthalein in the amount of 6 mg. is then injected into the buttock, and the urine collected: (1) for first appearance of color, (2) one hour after the injection and (3) two hours after the injection. The generally accepted normal limits are: (1) an excretion time of from ten to fifteen minutes, (2) an excretion of from 40 to 60 per cent during the first hour and (3) from 20 to 25 per cent during the second hour. The total for the two hours is normally from 60 to 85 per cent.

Observations.—Of thirty-three epileptic persons, fourteen (nos. 3, 9, 12, 17, 20, 24, 28, 29, 32, 45, 50, 52, 62 and 63) excreted less than 60 per cent of phenolsulphonphthalein in two hours. There was no delay in the first appearance of color.

THE TWENTY-FOUR HOUR URINE

The routine procedure was followed in the examination of the twenty-four hour specimen of urine, including total quantity, color, turbidity, reaction, specific gravity, albumin, sugar, acetone, diacetic acid and indican and microscopic examination of the centrifugated sediment. The methods employed were heat and acetic acid for albumin, Benedict's procedure for sugar, the Lange test for acetone, Gerhardt's test for diacetic acid and Obermeier's test for indican.

Observations.—Of sixty-one patients, ten (nos. 3, 7, 12, 13, 17, 32, 33, 54, 57 and 73) showed albumin or casts or both in a twenty-four hour specimen of urine. There were marked variations in the total quantity and specific gravity, probably dependent on diet and the amount of ingested fluids, the total quantity and the specific gravity being inversely proportional to one another in most cases.

URINE VOIDED IMMEDIATELY AFTER SEIZURE

The urine of three epileptic patients (nos. 8, 10 and 27) was collected immediately after seizure. Albumin and casts were present in the urine of all three and sugar in that of one (no. 27). None had shown any albumin, sugar or casts in one or more previous or subsequent interparoxysmal twenty-four hour specimens of urine.

It is interesting to note the changes in the urine of patient 27 (table 8). It will be seen that four hours after a seizure there was a marked rise in specific gravity accompanied by the appearance of albumin, sugar

TABLE 8.—*Changes in Urine of Patient 27*

Hours After Seizure	Reaction	Specific Gravity	Albumin	Sugar	Casts
¼	Acid	1.010	0	0	0
2	Acid	1.008	0	0	0
4	Acid	1.030	+	+	Hyaline and granular
24	Acid	1.004	+	0	0
28	Acid	1.008	+	0	0

and casts. All but the albumin had returned to the one-fourth hour state after twenty-four hours. No other abnormalities were noted.

Review of the Literature.—Novick [22] and others have reported post-seizure observations. Thus, in a study of sixty patients, Novick found that two-thirds showed albumin and casts after every seizure. These constituents persisted for from twenty-four to forty-eight hours after an attack in some cases. Bisgaard [23] found marked fluctuations in the ammonia content of urine in epileptic patients due to some metabolic disturbance. This appeared to be associated with a predisposition to spasm.

FRACTIONAL URINE STUDIES (QUANTITY AND SPECIFIC GRAVITY)

The following figures are based on fractional urine studies on thirty epileptic persons over a twenty-four hour period. The method followed was patterned after that of Mosenthal. Instead, however, of starting

22. Novick, N.: The Frequency of Albuminuria with Casts in Epileptics Following Convulsive Seizures, Arch. Neurol. & Psychiat. **4**:546 (Nov.) 1920.

23. Bisgaard, A.: Reaction of Urine in Relation to Epilepsy, Hospitalstid. **66**:502, 1923; abstr., J. A. M. A. **81**:1650 (Nov. 10) 1923.

day collection at 8 a. m. and night collection at 10 p. m., the hours were modified so as to conform more readily to hospital routine.

Observations.—In ten of the thirty patients (nos. 4, 24, 26, 36, 38, 48, 60, 65, 68 and 70), the total quantity of night urine exceeded 600 cc. This figure is taken as the high limit of normal because of the two additional hours of night collection by the method used as compared with that of Mosenthal. This amount is a fair average of the amounts usually passed between 7 p. m. and 7 a. m. by a healthy man on his usual diet. None of the ten patients gave evidence of renal involvement in the routine examinations of twenty-four hour urine or in the blood chemistry.

In only four patients (nos. 34, 37, 51 and 54) did fixation of specific gravity occur (i. e., variations between extremes of less than 0.009). One of these (no. 51) can be excluded because it was impossible to collect all of the two hour specimens. The specific gravity, though fixed, was high. As in all of these cases, the fluid intake was low. This observation appears to be of no significance.

INFLUENCE OF SALT-POOR DIET ON THE URINE

The effect on the blood chemistry of a salt-poor diet for seven days was shown in preceding paragraphs. The Volhard-Arnold method of determination of chloride was used.

Steyrer [24] gave from 6 to 22 Gm. as the normal range of sodium chloride excretion in healthy persons on a full diet. Yet thirty (nos. 3, 4, 6, 8, 10, 11, 16, 17, 19, 20, 21, 24, 25, 27, 28, 31, 33, 35, 36, 40, 48, 50, 53, 55, 57, 60, 61, 65, 69 and 70) of the fifty-four epileptic persons studied excreted more than 22 Gm. on one or more of the salt-poor days. The effect of salt restriction was generally manifested both in the reduction of the total quantity of urine and in the diminished excretion of sodium chloride. Some patients, whose excretion of sodium chloride was originally within normal limits, began to excrete in increased amounts (nos. 4, 8, 10, 11, 16, 17, 19, 33, 38, 40, 55, 60 and 61). It may be that these obtained salt in spite of all precautions. This explanation seems most likely in the cases in which the sudden increase occurred at or near the sixth day, as it was just about this time that many patients complained of being "salt-hungry." The patients (nos. 3, 7, 8, 10, 13, 17, 25, 27, 32, 33 and 57) who had shown albumin or casts in previous examinations of the urine showed no significant changes. The total amount of urine and the chloride excretion were, as is usually the case, directly proportional to one another. Some patients (nos. 7, 13, 16, 45 and 71) excreted small amounts of sodium chloride.

24. Steyrer, A.: Ueber osmotische Analyse des Harns, Beitr. z. chem. Physiol. u. Path. **2**:318, 1902.

SUMMARY OF OBSERVATIONS ON RENAL FUNCTION

Taken in conjunction with the data on the blood chemistry, the following data on renal function may be given in summary.

1. A rather high percentage of epileptic persons showed a low phenolsulphonphthalein excretion without any significant changes in the values for the nitrogenous constituents of the blood.

2. Of those epileptic persons who had a high chloride content in the blood before the inception of a salt-poor diet, most showed a persistingly high content after six days. This tendency appeared for the most part in patients having a normal phenolsulphonphthalein excretion and no urinary evidence of renal disease in the interparoxysmal periods. High chlorides persisted, however, in two of three patients (nos. 8 and 10) whose urine showed albumin or casts directly after a seizure.

3. While the effect of a salt-poor diet in these epileptic persons was generally a reduction in the chlorides of the blood and urine, in a large percentage the chlorides persisted high even after six days. It is questionable whether or not this salt retention is significant. It does not appear to be connected with renal damage as gaged by present methods. Whether or not it is related to seizures will perhaps be more evident when that subject is taken up.

4. It seems that though slight and repeated renal insults may occur with each seizure it probably takes a great many years of frequent seizures to produce any serious damage. The exceptions may be patients with previously damaged kidneys. This observation is also of interest in connection with studies of blood pressure.

There appeared to be no unusual features about the fluid intake and urinary excretion in this series. There was, however, a general tendency to large fluid intake after recovery from a seizure. Individual discrepancies were probably due to errors incumbent on handling this type of patient.

OTHER OBSERVATIONS

SUGAR TOLERANCE

None of the forty-seven epileptic patients in this series had diabetes mellitus or insipidus. This knowledge was based on two or three estimations of the blood sugar during fasting, numerous examinations of the twenty-four hour urine and the clinical history. The unusual capacity for food which most of these patients possessed in the interparoxysmal periods often left the impression that perhaps this was compensatory for the period of catabolic activity represented by a seizure. Their average food requirements far exceeded those of any similar group of approximately the same size and age in any other of the hospital wards. Presumably, in any severe muscular activity, carbohydrate is most readily available and quickly burned up. Yet these patients with frequent

seizures not only did not lose weight but gained. Perhaps they had some unusual capacity for storing carbohydrate or making it out of fat or protein. This might or might not be associated with endocrine disturbance. Accordingly, an endeavor was made to ascertain how many epileptic persons could tolerate 200 Gm. of dextrose (i. e., without the appearance of sugar in the urine within two hours). This amount is from 80 to 100 Gm. more than that used in the tests based on 1.75 Gm. of dextrose per kilogram of body weight (Killian) or on the ingestion of 100 Gm. regardless of weight. The average body weight of this group (stripped) was approximately 140 pounds (63.5 Kg.).

Observations.—Of forty-seven epileptic patients, only fifteen (nos. 1, 2, 16, 19, 21, 25, 26, 31, 35, 48, 52, 53, 60, 62 and 63) excreted dextrose before the end of the two hour period. Of these, three (nos. 1, 21 and 53) showed it in only one of the eight specimens. Seven (nos. 1, 2, 16, 19, 35, 52 and 60) had previously shown a normal and two (nos. 62 and 63) a low phenolsulphonphthalein excretion. On five (nos. 21, 25, 26, 31 and 48) examinations were not done. Of the thirty-three not excreting sugar, eleven showed a low phenolsulphonphthalein elimination.

Comment.—The interpretation of these figures must be left for another part of this paper. It seems certain, however, that many epileptic patients can tolerate and store large amounts of carbohydrate. At least, it may be said that not all healthy adults of 140 pounds' weight (63.5 Kg.) can ingest 200 Gm. of dextrose without its subsequent appearance in the urine in one of the fifteen minute specimens. Moreover, the phenolsulphonphthalein test did not show a lower degree of renal impairment in those who failed to excrete sugar. This tends to rule out the occasional case of high renal threshold for dextrose associated with nephritis and hypertension.

THE SPINAL FLUID

Great difficulty was encountered in obtaining consent for lumbar puncture. Even though this procedure was left to the end of the long series of examinations, consent could be obtained from only twenty-five patients. Of these, three (nos. 5, 16 and 54) gave a positive Wassermann reaction. Patient 16 had a 4 + Wassermann reaction of the blood and was under antisyphilitic treatment at the time.

The general technic employed in carrying out the Wassermann test has been described. In the case of spinal fluid, however, the amounts were larger, and no inactivation was used.

The Lange colloidal gold test was carried out on all fluids not containing erythrocytes. The colloidal solution was prepared in the laboratory under most scrupulous conditions and was subjected to the usual

tests. Known control spinal fluids were set up each day. One patient (no. 5) who had a positive Wassermann reaction also showed a paretic type of curve.

It is interesting to compare these figures with those on the first eighty spinal fluids of nonepileptic patients submitted to the laboratory. Of these, nineteen gave a positive Wassermann reaction, while nine gave a Lange curve of syphilitic type, nine, a curve of the paretic type and one, a curve of the meningitic type. One might infer with some degree of accuracy, therefore, that syphilis of the nervous system is not present to any greater extent in epileptic patients than in patients with other nervous diseases.

No manometric studies of spinal fluid pressure were made, but there appeared to be no marked changes in pressure in any case as judged by the rapidity of drip through the lumbar puncture needle. All fluids were withdrawn during the interparoxysmal period.

Review of the Literature.—Patterson and Levi [25] studied the spinal fluid of fifty epileptic patients and found that the cytology, p_H, sugar, albumin, urea and chlorides were within the normal range. One patient with hyperglycemia had a parallel hyperglycorrhachia. The ninhydrin reaction was positive in a number of patients showing no other abnormality than the colloidal gold curve. Patterson and Levi also found an unusually high percentage of colloidal gold curves of the cerebrospinal syphilitic type, but it is possible that this was due to faulty technic—for example, they used only singly distilled water.

Phosphates, traces of albumin and choline (Donath) have been reported found in the epileptic spinal fluid. Dide and Sacquepee-Pellegrin produced convulsions by injecting the spinal fluid of an epileptic patient into a guinea-pig. This "hypertoxicity" was especially evident immediately after an attack. Tiburtius produced similar results by the use of brain substance triturated with serum. It is questionable whether suitable controls were used in this work.

Laures and Gascard [26] found a marked rise in the urea content of the cerebrospinal fluid during an epileptic seizure.

Baylac and his co-workers [27] observed an increase in the number of polymorphonuclears in the spinal fluid during status epilepticus. This was accompanied by a marked hemoclastic crisis.

---

25. Patterson, H. A., and Levi, P.: The Spinal Fluid in Epilepsy, Arch. Neurol. & Psychiat. **15**:353 (March) 1926.

26. Laures, G., and Gascard, E.: Urea in the Spinal Fluid in Epilepsy, Presse méd. **28**:396, 1920; abstr., J. A. M. A. **75**:509 (Aug. 14) 1920.

27. Baylac; Bize, and Stillmunkes: Polynucleosis of Cerebrospinal Fluid in Epilepsy, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:154, 1923; abstr., J. A. M. A. **80**:1545 (May 26) 1923.

Comment.—The observations on the spinal fluid in the epileptic persons studied are not specific. The deviations from the norm can be accounted for by a co-existing and probably independent cause.

PROTEIN SENSITIZATION

The profound and sudden physical paroxysms into which the epileptic person is thrown were not infrequently ascribed by the patients to some food idiosyncrasy. This inference was due in many instances to the disagreeable gastric sensation constituting the aura. Clinically, the sudden change from comparative normality to a condition of violent physical distress and as sudden return to normality with little or no knowledge of what has happened suggests the liberation of some toxic substance possibly cumulative in its effects. According to present knowledge, if this is in the nature of a simple food idiosyncrasy, the most likely element at fault is protein. This does not refer to toxic split protein products, which in later investigations I found to be the basis of a widely accepted theory as to the etiology of epilepsy.

Accordingly, forty-four patients in this series were submitted to cutaneous tests, in which fifty-six of the common food and bacterial proteins were employed. The bacteria were included in an endeavor to rule out sensitiveness to some cryptogenic infection. The scratch method and tenth-normal sodium hydrate, together with proper controls, were used in each case.

The foods employed included: bluefish, egg white, egg yolk, navy bean, cheese (mixed), egg plant, cow's milk casein, egg, beef, cow's milk, corn, codfish, spinach, veal, goose feather, cat, cat hair, horse hair, chicken feather, dog hair, wheat, mustard, tea, coffee, cow's milk albumin, orange, almond, peanut, lobster, onion, mackerel, buckwheat, grapefruit, turkey, rye, tomato, salmon, chicken, white potato, lima bean, sweet potato, lamb, rice, pork and haddock.

The bacteria included: *Streptococcus nonhemolyticus, Pneumococcus III, Pneumococcus II, Pneumococcus I, Bacillus diphtheriae, Staphylococcus citrus, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus albus, Micrococcus catarrhalis* and *Staphylococcus aureus.*

Observations.—There was not a single instance of a clearcut skin reaction to any of the proteins used. Whenever there was doubt, the cutaneous was checked up by the intracutaneous method.

In the course of this work, an effort was made to detect in each of these patients a possible sensitiveness to homologous serums. For this purpose three serums were prepared from blood withdrawn from as many epileptic persons (having negative Wassermann tests), immediately after seizure. The serum of a normal person being used as a control, the serums were tested separately by both the cutaneous and the intracutaneous methods on seventy-three epileptic persons. In no

case was there any local or systemic reaction. While not conclusive, these results cast some doubt on the liberation of a peculiar protein or "toxic" substance into the blood stream during a seizure. Complement fixation tests were made in an effort to detect this substance, the antigen used being dried multiple epileptic serums. No conclusive results were recorded, but this work will bear repetition. Postseizure epileptic serum was also injected into guinea-pigs and rabbits in amounts varying from 0.5 to 5 cc., without any constant results.

Review of the Literature.—Ward and Patterson,[28] studying 1,000 epileptic patients at the Craig Colony and New Jersey State Village for Epileptics, reported positive reactions in 46.9 per cent, as compared with 8 per cent in 100 controls.

Howell [29] found all but one of eleven epileptic children sensitive to one or more food or bacterial proteins. On the other hand, Cohen and Lichtig [30] tested each of ten epileptic children with 128 proteins, but found no reaction which could be correlated with their convulsive seizures.

Wallis and his co-workers [31] tested 122 epileptic patients and found that forty-six reacted to the following substances in order of frequency: peptone (twenty-eight), cereals (fifteen), fish and meat (fifteen), vegetables (nine), eggs (nine) and milk (three). The reactions of a group of 100 controls were essentially negative. These investigators selected healthy, obese, nonexcitable epileptic persons who did not respond readily to bromides. It was found that the patients were most sensitive when not fatigued and just before an attack. The sensitivity seems to vary in the same person, often disappearing after an attack.

Von Leeuwen and Leydner [32] isolated a muscle-stimulating substance from the blood of epileptic patients and from cases of asthma, urticaria and migraine, which are often regarded as allergic in origin.

McCready and Ray [33] reported the cases of four patients in whom epilepsy was apparently due to a definite allergy toward food or serum protein.

---

28. Ward, J. F., and Patterson, H. A.: Protein Sensitization in Epilepsy, Arch. Neurol. & Psychiat. **17**:427 (April) 1927. This reference was found in a bibliography given at the time of the Ward-Patterson article.

29. Howell, L. P.: Differentiation of Skin Eruptions in New-Born (a study of fourteen epileptic children), Ohio State M. J. **19**:417, 1923.

30. Cohen, M. B., and Lichtig, H. A.: Protein Sensitization and Epilepsy, Ohio State M. J. **20**:571, 1924.

31. Wallis, R. L. M.; Nichol, W. D., and Craig, M.: The Importance of Protein Hypersensitivity in the Diagnosis and Treatment of a Special Group of Epileptics, Lancet **1**:741, 1923.

32. Von Leeuwen and Leydner, quoted by Miller, J. L.: Evidence that Idiopathic Epilepsy is a Sensitization Disease, Am. J. M. Sc. **168**:645, 1924.

33. McCready, E. B., and Ray, H. M.: Allergy as a Factor in the Etiology of Idiopathic Epilepsy, M. J. & Rec. (suppl.) **120**:117, 1924.

Crockett [34] reported the cases of seven epileptic persons (one definitely tuberculous) who were cured or relieved by injections of tuberculin. In three other patients there was no change. Hamilton,[35] Pearce,[36] Gudder,[37] Chambrelet,[38] Terillon,[39] Weir Mitchell [40] and others reported the effect of intercurrent infections and of pregnancy on epilepsy. The reports are conflicting and somewhat confusing because of inadequate follow-up data.

Others have injected epileptic serum into normal human beings and animals without producing convulsions. Ceni, however, reported rather severe reactions in epileptic persons, though sometimes a marked improvement was noticed.

Comment.—The great difficulty in the interpretation of protein sensitization studies on epileptic patients is probably due to:

1. Technic. The high percentage of positive reactions reported by some needs further corroboration.

2. Confusion of the existence of a state of allergy with the pathogenesis of epilepsy. The two conditions might well be entirely independent of each other. Moreover, few authentic cases of permanent cure (five years or over) have followed desensitization or removal of the offending protein.

3. In the case of children, figures must be regarded with some allowance for the natural hypersensitiveness of children, as pointed out by Walker,[41] Rackemann,[42] Latham and Coke [43] and others.

THE SPUTUM

Interparoxysmal Period.—The sputum of sixty-one epileptic patients was studied especially as to the presence of (1) tubercle bacilli, (2) unusual type of flora and (3) crystals. Other abnormalities, if present,

34. Crockett, J.: Tuberculin in Epilepsy, Brit. M. J. **1**:458, 1921.

35. Hamilton, A. S.: The Effect of Intercurrent Disorders on Pre-Existing Epilepsy, J. A. M. A. **53**:1902 (Dec. 4) 1909.

36. Pearce, F. S.: The Protein Influence of Pregnancy on Idiopathic Epilepsy, M. & S. Rep. City Hospital **76**:4, 1897.

37. Gudder: The Influence of Pregnancy on Epilepsy, J. Nerv. & Ment. Dis. **19**:65, 1892.

38. Chambrelet, J.: De l'épilepsie pendant la grossesse—son influence sur l'état de santé de l'enfant, J. de méd. de Bordeaux **29**:497, 1899.

39. Terillon: Note sur un cas d'épilepsie d'origine utérine, Ann. de gynéc. et d'obst. **16**:401, 1881.

40. Mitchell, Weir, quoted by Hamilton (footnote 35).

41. Walker, quoted by Longcope, W. T.: Anti-Anaphylaxis and Desensitization, Physiol. Rev. **3**:240, 1923.

42. Rackemann, F. M.: A Clinical Study of One Hundred and Fifty Cases of Bronchial Asthma, Arch. Int. Med. **22**:517 (Oct.) 1918.

43. Latham, A., and Coke, F.: Sensitization in 270 Cases of Asthma, Practitioner **109**:121, 1922.

were noted. The procedure adopted was to examine three or more early morning specimens that were received at the laboratory before 9 a. m. In a few instances only one specimen was obtained. The Ziehl-Neelsen method was used for the detection of tubercle bacilli. Under flora, the "usual type" refers to the organisms seen in the smear stained for tubercle bacilli and includes such forms as pneumococci, streptococci, staphylococci and occasionally *Micrococcus tetragenus*. As these organisms were identified morphologically, no attempt was made to ascertain anything other than the predominance or exclusive presence of any one type.

Paroxysmal Period.—An attempt was made to ascertain whether the profuse salivation during a paroxysm was purely a nervous phenomenon or an attempt to rid the body of some toxic substance. The sputum of ten different epileptic patients was collected during and immediately after a paroxysm. After filtration through a Berkefeld filter, a 1 cc. sample of each sputum was injected subcutaneously into a healthy guinea-pig weighing approximately 250 Gm. In no instance was there any local or systemic reaction within twenty-four hours. The experiment was repeated in most instances with unsterile, unfiltered sputum, with like results. A batch of grouped filtered sputums was made up, and intracutaneous inoculations were made in twenty-five epileptic patients, including those who had furnished the specimens. No reaction was obtained.

Summary.—No tubercle bacilli or other abnormal elements were found in the sputums of sixty-one epileptic patients. The detection of a toxic substance by the biologic method was unsuccessful, but the limited number of experiments warrants further study.

Comment.—The negativity of these observations is of interest in a consideration of the bacterial and toxic theories as to the causation of the epileptic fit.

THE FECES

Casual fecal specimens of sixty epileptic patients were examined. There were no restrictions as to diet. The benzidine and guaiacum tests were used for occult blood, and the results recorded as positive when both tests agreed. The simple emulsion in saline solution and the salt saturation methods were used for the detection of ova. The usual technic for food digestion was followed, described under the Schmidt diet in subsequent paragraphs. Estimation of the predominating flora was made by simple smear and Gram's stain. The types of gram-positive organisms (spore-bearers, streptococci, etc.) were not recorded. The following outline covers the general procedure:

1. Gross examination of feces: Amount, color, odor, consistence, reaction, mucus, pus, blood, tissue fragments, calculi, bile, parasites.

2. Chemical examination: Benzidine, guaiacum and bichloride tests.

3. Microscopic examination: Protein, fat, carbohydrate digestion, ova, yeasts, molds, *Sarcinae*, crystals, tissue elements, flora.

Color.—Three patients (nos. 34, 60 and 64) had stools of an unusual color: two, black and one, reddish brown. The latter (no. 64) owed the color to the presence of gross blood apparently associated with hemorrhoids.

Consistence.—Twenty-three patients had a hard, constipated type of stool, while seven had fluid feces (i. e., small solid particles floating in an abundance of fluid).

Reaction.—All specimens were amphoteric to litmus.

Gross Blood.—In one specimen only (that of no. 64) was gross blood evident.

Occult Blood.—Although present in many, occult blood was of no significance because of the meat-containing diet. Yet it is interesting to note how many patients on a similar diet gave negative benzidine and guaiacum tests.

Ova and Parasites.—All specimens were negative for ova and parasites.

Food Digestion.—There were seven persons (nos. 22, 23, 49, 55, 57, 61 and 62) with poor protein digestion, as evidenced by the presence of many intact, well striated voluntary muscle fibers. The report of this observation may be open to criticism. It has been my experience, however, that the stools of a healthy person without dietary restrictions rarely shows more than an occasional well striated muscle fiber, unless the meat has been poorly chewed or ingested in excess. Moreover, many of the epileptic persons studied have stated that they feel distinctly better on a meat-free diet.

Flora.—As the reports were based merely on morphology, no definite conclusions were reached.

Digestive Power of the Intestine.[44]—The technic of Schmidt was followed in the tests for digestive power of the intestine and a specimen of the stools collected after seventy-two hours. On the iodine (carbohydrate) and acetic acid (fatty acids) slides, it was sometimes difficult to judge accurately as to the efficacy of digestive power. These cases were marked "fair."

After three days of the Schmidt-Strasburger diet, two of twenty-three patients (nos. 8 and 27) showed 30 per cent of gas formation by the twenty-four hour fermentation test, an observation that suggests

44. Schmidt and Strasburger: Die Faeces der Menschen, Berlin, A. Hirschwald, 1901. Schmidt: Die Funktionsprüfung des Darmes, Munich, J. F. Bergmann, 1904.

imperfect intestinal digestion. One patient (no. 21) showed poor digestive capacity for protein. The casual stools of patients 8 and 21 had previously been classified as abnormal.

Summary.—In all, twelve specimens of stools were classified as abnormal, based on color, consistence, the presence of blood or evidence of faulty food digestion.

Review of the Literature.—Cobb,[45] studying the fecal acidity of fifty epileptic girls and women, found a mean acidity of 5.22 (in terms of normal sodium hydrate necessary to neutralize the acids extracted from 100 Gm. of feces). This figure was subject to much variation in individual cases and had no relation to the number of paroxysms.

Comment.—Many epileptic patients, probably of a certain type, appear to be benefited by colonic eliminative measures or dietary limitations or both. The abnormal fecal observations in this series may point, in these selected cases, to the bowel as a contributory factor in the pathogenesis. While the constipated patients felt better after catharsis, there was no appreciable effect on the frequency of seizures.

CARDIAC FUNCTION [46]

The procedure followed in the test of fifty-eight epileptic persons for cardiac function was as follows: The blood pressure, pulse and heart were examined under restful conditions. The patient then hopped fifty times, and the pulse and heart were reexamined.

Pulse Rate.—Five patients (nos. 4, 5, 10, 26 and 45) had a pulse rate of 64 or less, suggesting a vagotonic state. This list was later supplemented by eight additional patients (nos. 6, 9, 20, 27, 28, 30, 60 and 61), making a total of thirteen who showed bradycardia. The bradycardia in one patient (no. 26) was accompanied by a marked sinus arhythmia. One patient (no. 39) had a persistent pulse rate of from 120 to 124. The exercise tolerance in nearly every case was good, there being only a slight increase in the pulse rate (patients 55 and 68 being the exceptions).

Cardiac Abnormalities.—Eleven patients exhibited deviations from the norm; one (no. 55) showed mitral stenosis; two (nos. 31 and 40), mitral insufficiency; two (nos. 26 and 69), bradycardia and sinus arhythmia (vagotonia); one (no. 4), reduplication of the second pulmonic sound and cardiac hypertrophy; one (no. 2), accentuation of the second aortic sound; one (no. 18), aortic dilatation, and three (nos. 36, 48 and 68), neurocirculatory asthenia.

45. Cobb, G.: The Fecal Acidity in the Insane Epileptic, J. Ment. Sc. **72**:83, 1926.

46. Dr. Hubert Mann gave careful attention to these studies.

Electrocardiographic Observations.—Left ventricular predominance was shown in seven patients (nos. 13, 16, 31, 35, 44, 62 and 63); right ventricular predominance in one (no. 7), and extrasystole in two (nos. 19 and 24). Of these, patient 31 had a mitral insufficiency.

Comment.—The general freedom from organic cardiac defects is surprising in view of the repeated cardiovascular strains to which the epileptic person is subjected during a paroxysm.

THE BLOOD PRESSURE

Diurnal Variations.—Records of blood pressure were made for twenty-nine epileptic patients during their usual daily hospital life, the blood pressures being taken before and after each meal, and on seizure-free days only. The first reading of blood pressure was done approximately one-half hour after the patient's rising, following the usual morning ablution and dressing.

From these rather meager records it was noted that the usual slight rises occurred in the afternoon, evening and after meals. In this respect there is no variation from the physiologic. Readings that were started but discontinued because of the occurrence of a paroxysm later in the day showed no essential changes, except when, by chance, they were taken just before a fit. In the latter case, the pressure was usually high (no. 24). Hourly studies during the waking period sometimes showed surprising variations (no. 2). One patient (no. 73) had severe nephritis of the arteriosclerotic type and also had what was apparently essential epilepsy.

Postseizure Variations.—Estimations of blood pressure were made on twenty-two epileptic patients immediately following seizure. As a basis for comparison, the average normal blood pressure of each patient is taken into consideration. In cases in which a rise occurred, readings were taken every five minutes until the return to the average normal figure. Five minute intervals were found sufficient, as minute readings (the cuff being left in place) gave essentially a repetition of the same pressure level.

It was found that in about one half of the patients studied the blood pressure returned to normal within fifteen minutes. One might say that this constituted an excellent clinical test for cardiac function. A few patients (nos. 4, 35, 47, 48, 68 and 71) exhibited slight if any rise in pressure. Others (nos. 65 and 67) had a prolonged elevated level from 106 systolic and 72 diastolic to 170 systolic and 136 diastolic (no. 65) and from 110 systolic and 70 diastolic to 164 systolic and 112 diastolic (no. 67). One patient (no. 63), whose temperature, pulse and respiration had been taken one-half hour before the seizure, showed no appreciable increase in the rectal temperature and a slight increase in the

pulse and respiration rates. Another patient (no. 52) had a normal blood pressure of 110 systolic and 80 diastolic just before a seizure.

In general, it might be said that the increase in blood pressure was proportional to the number and severity of the seizures. It would seem, therefore, that the rise was due at least in part to muscular exertion. That this is not the sole explanation will be evident from data submitted in connection with petit mal attacks.

Review of the Literature.—Addis [47] observed variations in blood pressure on normal soldiers of approximately the same age as the epileptic persons studied in this paper (from 21 to 31). Comparing the basal state, that found after an all night sleep and before breakfast or exercise, to the day state, he observed that the basal norm of seventy-six persons was 99 systolic and 71 diastolic, with a pulse rate of 63, and that the day norm of 300 persons was 127 systolic and 78 diastolic, with a pulse rate of 80.

Studying the effects of food, exercise and excitement, the same author concluded that food has little or no effect. Exercise in the form of 100 hops raised the systolic pressure from 125 to 156, the rise being most marked during the first period. The degree of change is proportionate to the level existing before exercise. My figures on epileptic patients in the postparoxysmal state show that the highest pressure is attained within the first five or ten minutes.

Brooks and Carroll,[48] studying three groups of patients with average basic afternoon systolic pressures of 142.5, 100 and 204.5, found that in relation to sleep, the greatest drop occurs within the first two hours. The greater the basic level, the greater is the drop. After the second hour, the pressure gradually rises. Tarchanoff [49] had previously obtained similar results in young dogs, and Brush and Fayerweather [50] in normal man.

Pollock and Treadway [51] studied forty-one epileptic patients of whom eighteen had systolic pressures of 120 or below and twenty-three, from 125 to 200. Of seventeen patients examined on the day of convulsion, seven had a systolic pressure above 135, and ten, below 120. The pulse pressure in all but eight patients varied between 40 and 50 mm. Of the

47. Addis, T.: Blood Pressure and Pulse Rate Levels: First Paper, Arch. Int. Med. **29**:539 (April) 1922; Second Paper, ibid. **30**:240 (Aug.) 1922.

48. Brooks, H., and Carroll, J. H.: A Clinical Study of the Effects of Sleep and Rest on Blood Pressure, Arch. Int. Med. **10**:97 (Aug.) 1912.

49. Tarchanoff, J.: Quelques observations sur le sommeil normal, Arch. ital. de biol. **21**:318, 1894.

50. Brush, C. E., and Fayerweather, R.: Observations on the Changes in Blood Pressure During Normal Sleep, Am. J. Physiol. **5**:199, 1901.

51. Pollock, L. J., and Treadway, W. L.: A Study of Respiration and Circulation in Epilepsy, Arch. Int. Med. **11**:445 (April) 1913.

eight with pulse pressure above 55 mm., five either were measured on the day of convulsion or had some cardiovascular disease. Many patients exhibited Traube-Hering waves, especially just preceding or following a fit and usually disappearing by the fifth day. The sequence of events leading up to a convulsion seemed to be a preliminary rise in blood pressure followed by a sudden drop, then a period of apnea followed by the fit. In the patients with petit mal and some with grand mal types of epilepsy, the blood pressure was low. During the convulsive period, the pulse was uniformly rapid.

With a view to a critical interpretation of the variations in blood pressure mentioned, it is interesting to note the observations of Alvarez [52] in 15,000 university freshmen. Among the men (6,000), he found a tension of more than 130 mm. of mercury in about 45 per cent, and of more than 140 mm. in 22 per cent. Among the women, 12 per cent had tensions exceeding 130 mm. and 2 per cent, exceeding 140. The pressures for men were grouped around 127 mm. at the age of 16, and around 118 at the age of 30. The pressures for women varied from 118 mm. at the age of 16 to 111 at 24 and 117 at 40 years.

Comment.—The interpretation of the variations in the blood pressure of the epileptic patient can be properly made only after due consideration of the variations in normal persons of the same age and sex. The only patient (no. 73) who had a persistent hypertension had an advanced cardiorenal condition to explain it. One can state with some certainty that the degree of rise in pressure, properly considered, is an indication of the physical severity of the fit. Compared with Addis' figures on the normal soldier, the rise in the epileptic patient is more than that produced by 100 hops of a normal adult man (31 mm.). This is probably not as significant as the fact that in a few exceptions there was little or no increase in pressure (nos. 4, 35, 47, 48, 68, 70 and 71). It is important to know why these patients showed no appreciable variation after a grand mal attack. Looking back on their tests for cardiac function one sees that patient 4 had bradycardia but fairly good tolerance of exercise; patient 35 had fair tolerance; patient 47 was normal; patient 48 had mild neurocirculatory asthenia; patient 68 had distinctly poor tolerance with an initial pulse rate of 100, and patients 70 and 71 were normal. Incidentally, patients 70, 68, 35 and 4 had some auscultatory cardiac signs which, at the time of examination, did not appear to be definitely due to organic disease.

The basal morning pressures and pulse rates in epileptic patients are comparable with those of Addis for the norm, except for the relatively high percentage of bradycardia in the epileptic patients. The occurrence

52. Alvarez, W. C.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923.

of a temporary heart block in the epileptic patient will be considered under pathologic studies. The effects of rest and exercise on the epileptic patient are essentially those on the normal man.

BASAL METABOLIC RATE

The Benedict type of machine (Sanborn) was used in the estimation of the basal metabolic rate (by indirect calorimetry). Basal conditions included fourteen hours of rest and abstinence from food plus one-half hour rest on the metabolism couch just before the test. The rectal temperature taken just before the rest period was normal in each instance. A separate room, remote from the wards and laboratory proper, was utilized. Ten minute readings with one minute checks served as an index to the reliability of a single test. All abnormal rates and obviously unreliable readings were rechecked by a second test.

Observations.—Six patients (nos. 3, 4, 35, 60, 61 and 62) showed abnormally high basal metabolic rates (+ 15 per cent or above). One of these patients (no. 4) had a persistent hyperpnea each time he underwent a test. It is interesting to note that eight patients (nos. 6, 9, 20, 27, 28, 30, 60 and 61) had definite bradycardia before the test, which was completed between 9 and 10 a. m. One (no. 6) had a pulse rate of 48 before the procedure began and 56 at its termination. Seven patients (nos. 1, 6, 17, 27, 39, 60 and 61) had respiratory rates of 14 or below. Four of them (nos. 6, 27, 60 and 61) also had bradycardia, although two (nos. 60 and 61) had moderately high metabolic rates.

As a basis for comparison, the first 250 patients (other than epileptic patients included in this paper) sent to the laboratory for a basal metabolic test were classified according to the diagnoses at discharge. It was found that there was a considerably lower percentage of high basal rates among the epileptic persons.

Review of the Literature.—Talbot and his co-workers [53] studied eleven children affected with idiopathic epilepsy and found the metabolic rate normal or elevated in all. Bornstein [54] reported a marked increase in metabolic rate after an epileptic attack, the increase remaining for twenty-four hours. Talbot and his co-workers found no evidence to support this contention. Bowman and Grabfield [55] found the metabolic rate to be from — 20 to — 21 per cent in three epileptic patients and normal in three others. No psychosis was present.

---

53. Talbot, F. R.; Hendry, M., and Moriarty, M.: The Basal Metabolism of Children with Idiopathic Epilepsy, Am. J. Dis. Child. **28**:419 (Oct.) 1924.

54. Bornstein, A.: Untersuchungen über die Atmung der Geisteskranken, Monatschr. f. Psychiat. u. Neurol. **24**:392, 1908.

55. Bowman, K. M., and Grabfield, G. P.: Basal Metabolism in Mental Disease, Arch. Neurol. & Psychiat. **9**:358 (March) 1923.

ROENTGENOGRAPHIC STUDIES IN EPILEPSY [56]

The Skull.—For the sixty epileptic patients, the procedure included the making of lateral and anteroposterior views of the skull on stereoscopic plates. For the lateral views, a 5 inch spark gap, 30 ma. and 26 inch distance from target to plate were used. The time of exposure in seconds corresponded to the interparietal measurement of the skull in inches. In the first exposure, the central ray was directed through a point 1 inch (2.5 cm.) anterior to the external auditory meatus. A second plate was made after the tube had been shifted 2½ inches (6.27 cm.) caudad and 15 degrees cephalad. For the anteroposterior views, a 5½ inch spark gap, 30 ma. and 26 inch distance from target to plate were used. With the nose and forehead of the patient on the table, the central ray was directed at the nasion. The time of exposure in seconds was one and a half times the distance in inches between the inion and the nasion. No intensifying screens were used.

For the 100 controls, the procedure included only lateral views. A 5 inch spark gap, 30 ma. and 84 inch distance were used, the central ray being directed at a point 1 inch (2.5 cm.) anterior to the external auditory meatus. The time of exposure in seconds corresponded to the interparietal distance in inches. Double intensifying screens were used.

The proper interpretation of a picture of the skull depends on (1) the technic employed and (2) the normal anatomic hindrances (i. e., overlapping of structures) and a thorough knowledge of the normal for a particular age and sex. As a guide in the proper interpretation of the anomalies in the skulls of epileptic patients, therefore, the skulls of 100 normal persons of approximately the same age as the epileptic patients were studied. The series of normal persons included doctors, attendants and patients without any known physical or mental disability, except as stated.

The anomalous observations in the skulls of the sixty epileptic patients may be classified from an anatomicopathologic standpoint as in table 9. Of sixty patients, forty-three showed what, at the time the pictures were taken, were considered departures from the usually accepted anatomic norms. After the work was completed, however, this opinion was modified by reason of the results obtained with the 100 normal subjects. Calcification or separation of the suture lines, slight irregularities in contour of the inner table, depressions, prominent diploe and calicification of the pineal body were among the unusual features noted. In five cases, the anatomic changes were apparently associated with a long standing injury of the head without subsequent epilepsy.

56. Dr. Frank Liberson gave scrupulous attention to this part of the work. The control studies were made entirely at his expense.

There was considerable variation in the size of the sella and the interclinoid space (as measured between the middle and posterior clinoids). The sella turcica varied from 6 by 4 by 9 mm. to 14.5 by 8 by 11 mm., the figures referring to length by depth by height. The interclinoid space varied from 0 to 10 mm., the former figure indicating no visible space, but not necessarily fusion of the bony processes.

Other Structures.—In fifty-five epileptics the thorax was studied. Of these, eighteen showed evidence of an active or healed pleuritic or pulmonary lesion. The latter in five or six instances (nos. 13, 17, 27, 45, 48 and 61) was distinctly tuberculous. Of thirty-five patients, one (no. 26) had a decided enlargement of one lobe of the thyroid gland. Of thirty-five patients, one (no. 26) showed evidence of a persistent thymus. Of fifty-nine patients, thirty displayed a definite dental patho-

TABLE 9.—*Anatomicopathologic Classification of Anomalies Encountered in Skulls of Epileptic Patients*

Anomaly	Patients
Increase in convolutional markings (nos. 3, 9, 10, 34 and 45)	5
Areas of increased density, of doubtful etiology (nos. 3, 5, 29, 37, 40, 43, 44, 51 and 63)	9
Areas of diminished density, of doubtful etiology (nos. 1, 12, 54 and 60)	4
Bridging of clinoids (nos. 6, 9, 13, 32, 39, 49 and 52)	7
Female type of skull (nos. 11, 13 and 40)	3
Acromegalic type of skull (nos. 9 and 65)	2
Brachiocephalic type of skull (no. 12)	1
Dolichocephalic type of skull (no. 60)	1
Syphilitic skull (nos. 3, 18 and 58)	3
Traumatic changes: hiatus or exostosis (nos. 5, 7, 13, 16, 20, 43, 57, 61, 67 and 70)	10
Evidence of increased intracranial pressure (nos. 7, 9, 10, 34, 57 and 62)	6
Calcification of pituitary gland (no. 25)	1
Pituitary tumor (no. 39)	1
Irregularity of internal table (nos. 47 and 52)	2
Irregularity of external table (no. 57)	1
Cerebral endothelioma (no. 62)	1

logic condition. This consisted chiefly of retained root and periapical abscess. Of thirty-six patients, two (nos. 1 and 27) showed an atrophic or undeveloped condition of one or both testicles. Examination of the gastro-intestinal tract was made in two patients (nos. 17 and 20) in whom there appeared to be some derangement, but no abnormal roentgenographic evidence was obtained. In one patient (no. 73), calcified flakes were found in the left and right posterior tibial arteries. The tracheal, radial and cerebral blood vessels showed no calcified deposits. This man had a marked generalized atherosclerosis.

Summary.—Deviations from the generally accepted anatomic appearance of the skull were found in forty-three of the sixty epileptic patients studied. In view of the surprising number of similar changes in many of the skulls of 100 normal persons, a definite opinion as to their clinical significance is unwarranted. The anthropologic types, the syphilitic skull, the traumatic skull, the pituitary tumor and the dural endothelioma are definite. These comprise twenty-two instances. The

morphologic variants (in seven patients) are suggestive only when taken in conjunction with other evidence. Epilepsy in the twelve patients with the traumatic or neoplastic type of skull could not in all instances be attributed to the lesion detected. Not infrequently, the pathologic changes were subsequent to the onset of the epilepsy. In other words, a man may have an old fracture or hiatus of the skull and epilepsy but both conditions be unrelated. Of the three patients with syphilitic skulls, two (nos. 18 and 58) had had negative results in serologic tests and one (no. 58) a negative result in the Wassermann test of the spinal fluid and a negative colloidal gold curve. Of the epileptic patients with positive results in serologic tests (nos. 16, 41 and 72), one (no. 16) showed some change in the skull; patient 72 was not studied. Three epileptic patients (nos. 3, 16 and 54) with positive results in tests of the spinal fluids all showed some changes in the skull. In no instance, however, was a definite diagnosis of syphilis made roentgenologically.

Review of the Literature.—The literature concerning the roentgenologic appearance of the skull in epilepsy centers attention chiefly about the bony structures in the region of the pituitary body. Schüller [57] stated that an intrasellar tumor is suggested by a widening and deepening of the sella, a thinning of the floor and a thinning, backward displacement and inclination of the dorsum which forms an acute angle with the planum sphenoidale. There is evidence of acromegalic change in the rest of the skull (thickening of the wall, bony ridges and enlargement of the pneumatic spaces). He also called attention to a localized thickening of the base of the skull and the frontal floor in epilepsy. Johnston,[58] in a study of 100 epileptic patients between the ages of 15 and 35, called attention to: (1) an overgrowth of the anterior and especially of the posterior clinoids, which are folded over and down on the pituitary gland; (2) a decided difference in the size of the pituitary fossa and gland; (3) a fossa largely or completely roofed over, the clinoids sometimes overlapping, and (4) an increased density of the bony structure forming the roof of the orbits, sphenoidal sinus and ethmoidal cells. The sphenoidal cells may be blocked with newly formed bone tissue. McKennan described as "local acromegaly" a hyperostosis of the clinoid processes, anterior fossa and sometimes the postclinoidal region. The plates of normal and acromegalic persons do not show these changes.

57. Schüller, A.: Roentgen Diagnosis of Diseases of the Head, Translation, St. Louis, C. V. Mosby Company, 1918.

58. Johnston, G. C.: The Radiography of the Pituitary in Its Relation to Epilepsy, Am. J. Roentgenol. (n.s.) **1**:172, 1914.

McKennan and his co-workers [59] believed that the frequency of attacks is more important than the duration of the epilepsy in the production of these bony changes. Timme [60] was of the opinion that roentgenographic changes in the sella are not indicative of a pituitary lesion. Munson and Shaw [61] found inconstant anatomic changes in the pituitary. Moreover, the former [62] investigated the sella turcica in autopsies of eighty-five unselected epileptic patients and found it varying greatly. While roofing may be present in the x-ray picture, the gland post mortem appears to be well exposed and free from pressure. The bony changes are such as might be seen in nonepileptic persons. Lisser and Nixon [63] reported six cases of epilepsy associated with dyspituitarism. Except for one patient who was distinctly acromegalic, the x-ray pictures of the skull were normal. Camp [64] pointed out the difficulties involved in the roentgenologic interpretation of pictures of the sella. Variations in the shape of the clinoids, union between them and bridging are apparently of no significance. Anton,[65] in a study of fifteen epileptic patients, described a relative hypertrophy of the cerebellum, which can be readily recognized in x-ray plates.

As to the relationship of dental pathology to epilepsy, Tracy [66] and Tholuck [67] were convinced of this possibility.

Harryman and Donaldson [68] studied the gastro-intestinal tract in 125 epileptic patients roentgenologically and found hypermotility of the large bowel in 50 per cent and normal motility in the remainder.

Comment.—The results of these detailed studies of the skulls of epileptic patients, as compared with the skulls of normal persons of the same age and sex, reveal a high proportion of pathologic conditions. The

59. McKennan, T. M. T.; Johnston, G. C., and Henninger, H.: Observations on Epileptics Chiefly from an X-Ray Standpoint, J. Nerv. & Ment. Dis. **41**:495, 1914.

60. Timme, W.: Clinical Features Accompanying Changes in the Sella Turcica, Arch. Neurol. & Psychiat. **2**:240 (Aug.) 1919; Arch. Ophth. **49**:268, 1920.

61. Munson, J. F., and Shaw, A. L.: The Pituitary Gland in Epileptics, Arch. Int. Med. **14**:393 (Sept.) 1914.

62. Munson, J. F.: The Pituitary Gland in Epileptics, Arch. Int. Med. **21**:531 (April) 1918.

63. Lisser, H., and Nixon, C. E.: Dyspituitarism and Epilepsy: A Report of Six Cases, M. Clin. North America **6**:1471, 1923.

64. Camp, J. D.: The Sella Turcica, Significance of Changes in Its Roentgenographic Appearance, J. A. M. A. **86**:164 (Jan. 16) 1926.

65. Anton, G.: Roentgenography of the Head in Epilepsy, Jahrb. f. Kinderh. **93**:69, 1920; abstr., J. A. M. A. **75**:1603 (Dec. 4) 1920.

66. Tracy, E. A.: Teeth Anomalies and Epilepsy, Dental Cosmos **69**:410, 1927.

67. Tholuck, H. J.: Dentistry in Epilepsy, München. med. Wchnschr. **70**:1199, 1923; abstr., J. A. M. A. **81**:1994 (Dec. 8) 1923.

68. Harryman, W. W., and Donaldson, S. W.: Radiologic Gastro-Intestinal Studies in Epilepsy, J. A. M. A. **81**:813 (Sept. 8) 1923.

uniformly unsatisfactory postmortem examination of the head may possibly be discounted by closer attention to roentgenographic detail during life. The question of pituitary epilepsy cannot be settled by roentgenographic studies alone. The technic and interpretation are subject to too much error. I have yet to see in my routine postmortem work a pituitary body encroached on by bony structure, except in the case of fractures of the base or, indirectly, when the pituitary itself is the seat of change. In his experimental work, Cushing produced epileptic convulsions in animals by means of partial hypophysectomy with its associated secretory insufficiency. Similar conditions in man have been reported in connection with epilepsy, some patients even having gustatory attacks referable to direct pressure of the pituitary on the adjacent uncinate cortex. The anatomic aspects of this little structure certainly make theories involving pressure seem plausible. Encased in a bony recess covered over by tough, unyielding dura, the gland and its intercavernous sinuses need little interference to cause malfunction. The larger anterior lobe is glandular and richly vascularized, while the posterior is small, nervous in structure and connected with the infundibulum and third ventricle. The highly complex nature of the pituitary suggests that slight changes are more likely to manifest themselves in other ways than by convulsions. At least, there is no justification for the assumption that it is responsible for more than a small proportion of epilepsies.

Again it is suggested that from an etiologic standpoint, there are many different conditions included under the term "epilepsy."

STUDIES OF THE SYMPATHETIC NERVOUS SYSTEM

The clinical phenomena seen in epilepsy seem to indicate that in its objective manifestations, at least, this disease is essentially a disturbance of the nervous system. Aside from evident gross lesions in the sensory or motor areas of the cortex or their respective pathways, there seems to be some evidence that the sympathetic nervous system is involved in one group of cases at present classified together with other types under the general term "epilepsy." There is probably a close relationship of this system to at least two of the ductless glands, the suprarenal and thyroid glands. Together, they provide a delicately balanced, highly sensitive mechanism capable of producing many of the peculiar physical and mental phenomena noted in epilepsy.

The sympathetic (vegetative) nervous system may be divided into:

1. The sympathetic proper, the fibers of which arise in the intermediolateral regions of the cord, passing out by the anterior roots to end in ganglions which send fibers to the smooth muscle, heart, blood vessels, secretory glands, etc. The afferent fibers conduct visceral sensations and referred visceral pain. The ganglions form a series in front of the vertebral column, one on either side.

2. The autonomic system or system of the extended vagus. The most important constituent is the vagus nerve. In the craniobulbar portion, fibers pass to the ciliary ganglion (constricting the pupil), secretory fibers to the submaxillary gland, stomach and intestines, inhibitory fibers to the heart, constrictors to the bronchi and motor fibers to the esophagus, stomach and intestines. In the sacral portion, fibers supply the descending colon, rectum, anus, bladder and genital system by way of the pelvic nerve. The autonomic ganglions are placed more peripherally than those of the sympathetic proper.

The entire sympathetic nervous system has three plexuses: cardiac, solar and hypogastric, which receive fibers from both the divisions described.

Physiologic evidence points to the maintenance of a constant balance between the sympathetic proper and the autonomic system during health. An imbalance manifests itself as an overactivity of the one or the other system, and these conditions are at present defined by the generally accepted terms "sympatheticotonia and vagotonia."

The clinical signs pointing to vagotonia are small pupils, salivation, flushing, sweating, clammy hands and feet, dermatographia, bradycardia, irregularity of respiration, bronchial asthma, hyperacidity, cardiospasm and pylorospasm, spastic constipation and sphincter contraction. Eosinophilia, pharyngeal anesthesia, respiratory arythmia, angina, tremor and urinary frequency may be present. Sympatheticotonia is characterized by dilated pupils, prominence of the eyes, dryness of the mouth and skin, tachycardia and alimentary glycosuria. Loss of hair and unexplained rises in temperature may occur.

The work of Eppinger and Hess and others has shown that when both systems supply the same structure their action is antagonistic. Thus, the sympathetic dilates the pupil, increases the heart rate and inhibits movements of the gastro-intestinal tract, an influence directly opposed to that of the autonomic system. Moreover, an increased tone in one system practically rules out an increased tone in the other. Thus, patients who are sensitive to pilocarpine are less sensitive to epinephrine.

In the experimental study of thirty-seven epileptic patients, I attempted to supplement the clinical features suggestive of sympathetic imbalance by observations of the effects of the so-called "sympathetic" drugs. Epinephrine (8 minims of 1:1,000 solution) stimulates the sympathetic system proper, causing tremor, rigor, sense of cold, polyuria, glycosuria and a rise in blood pressure. Pilocarpine ($\frac{1}{8}$ grain) stimulates the autonomic system, causing salivation, nausea, sweating, flushing and fall in blood pressure. Atropine ($\frac{1}{100}$ grain) paralyzes the autonomic system, as evidenced by dryness of the mouth and throat, palpitation and oppression. The dosage decided on in the study was the

smallest consistent with a slight response in a normal man, weighing approximately 65 kilograms. Those who were excessively stimulated by the epinephrine or pilocarpine were considered tentatively as belonging to the sympatheticotonic or vagotonic group.

It is expedient to consider the effects of all three drugs together (pilocarpine and atropine, as vagotonic stimulant and paralyzant, respectively; epinephrine as a sympathetic stimulant). These observations were recorded without any reference to the clinical status of the patient. The results may be tabulated as follows:

Observations.—Eighteen patients (nos. 5, 7, 13, 17, 20, 24, 25, 27, 29, 31, 32, 39, 40, 45, 47, 50, 63 and 68) manifested an excessive response to pilocarpine, as displayed by salivation (50 cc. or more), perspiration, lowered blood pressure or bradycardia. Of these, two (nos. 25 and 27) were borderline cases. Six (nos. 20, 24, 31, 32, 47 and 50) also exhibited a response to epinephrine. Of the vagotonic types enumerated, fifteen (nos. 5, 13, 20, 24, 25, 27, 29, 31, 32, 39, 40, 45, 47, 50 and 63) gave no evidence of reaction to atropine, thus suggesting a fair degree of vagotonicity.

Excessive response to epinephrine, as displayed by tremor, polyuria or rise in blood pressure, occurred in twenty-two patients (nos. 2, 6, 10, 11, 20, 21, 22, 24, 26, 31, 32, 34, 35, 36, 47, 50, 58, 60, 62, 65, 69 and 71). Three were deemed to be doubtful (nos. 60, 65 and 69). Of the twenty-two patients, six (nos. 20, 24, 31, 32, 47 and 50) also gave an excessive response to pilocarpine. Six (nos. 2, 26, 31, 35, 60 and 62) showed an alimentary glycosuria during the sugar tolerance tests also suggestive of sympatheticotonia. Three (nos. 35, 60 and 62) also had an increased basal metabolic rate.

Of the vagotonic types, clinical evidence, mainly in the form of bradycardia and sinus arhythmia, supported the laboratory results on only five patients (nos. 5, 7, 13, 24 and 45). Only two of the sympatheticotonic types had clinical support for the laboratory data (nos. 6 and 20).

Review of the Literature.—Popea and his co-workers[69] studied the rôle of vagotonia in forty-five epileptic patients. By paralyzing the vagus with atropine, seizures were produced after ten minutes in six persons. In sixteen other persons, convulsions occurred within twelve hours. These authors concluded that an epileptic seizure may be accompanied or even preceded by hypervagotonia, but that the latter is not a causative factor.

69. Popea, A.; Eustatziu, G., and Holban, G.: Rôle of Hypervagotonia in the Epileptic Seizure, Compt. rend. Soc. de biol. **92**:1170, 1925; abstr., J. A. M. A. **85**:73 (July 4) 1925.

Tinel [70] likened the epileptic paroxysm to a state of sensitiveness or hypervagotonia, as shown by the presence of alimentary disturbance and increased oculocardiac reflex. During the quiescent period, a hypervagotonia or sympatheticotonia may exist.

Comment.—Clinical evidence favored an existing abnormal state of vegetative nervous system in only seven patients. Laboratory studies raised the number to thirty-five or forty (five being doubtful) out of a total of eighty on whom tests were made (on thirty-three with pilocarpine; on forty-seven with epinephrine). Approximately one half of the patients tested were either sympatheticotonic or vagotonic. Six patients responded to both types of drug stimulants. The prodromal and postseizure signs and symptoms of an epileptic paroxysm include many of those characteristic of hypervagotonia. In many instances, however, the interparoxysmal period is characterized by a hypersympatheticotonic state. Thus, clinical observations are not at all inconsistent with the laboratory observations. A delicate balance is maintained by the antagonistic action of the autonomic (vagotonic) and sympathetic systems at the most quiescent or normal intervals of the interparoxysmal stage. At unknown intervals preceding and following a seizure, this balance seems to be disturbed and one system of the other predominates its action. It is not unlike a delicately adjusted thermostat that suddenly gets out of order. This state in the epileptic might be termed "vegetative instability," and the results of the drug tests vary, depending on when the tests are made. If this supposition is true, the cause of this instability still remains to be expained and its relative importance in the production of a seizure properly interpreted.

SUMMARY OF LABORATORY OBSERVATIONS ON SEVENTY-THREE EPILEPTIC PATIENTS

1. Gastric Studies[1]
   Complete absence of free hydrochloric acid in 11 per cent of the 53 patients studied (nos. 7, 11, 24, 31, 50, 57 and 60).
2. Blood
   A. Formed Blood Elements, Interparoxysmal Period (57 patients)
      Low platelet count (nos. 16 and 65) 2
      Prolonged coagulation time 10
      (nos. 2, 5, 19, 20, 21, 28, 49, 52, 61 and 65)
      Increased resistance of erythrocytes (no. 65) 1
      Leukocytosis (nos. 22, 46 and 54) 3
      Leukopenia (nos. 16, 19, 34, 37, 48, 53, 68 and 70) 8
      Lymphocytosis (nos. 1, 6, 17, 20, 27, 28, 32, 39, 44, 49 and 50) 11
   B. Formed Blood Elements, Paroxysmal Period (12 patients)
      Leukocytosis (nos. 9, 13, 31, 57, 61, 63, 64 and 65) 8
      Lymphocytosis (nos. 4, 9, 13, 31, 56, 57, 58, 61, 63, 64 and 65) 11

70. Tinel, J.: Nouvelles conceptions et nouveaux traitements de l'epilepsie. Médecine **3**:366, 1922.

C. Chemistry, Interparoxysmal Period (55 patients)
Dextrose
Hypoglycemia (nos. 9, 10, 13, 28, 44, 45, 49 and 63) 8
Hyperglycemia (nos. 21, 24, 37, 40, 58 and 65) 6
Uric Acid: Increase (nos. 2, 5, 21, 24, 25, 34, 36 and 37) 8
Chlorides: Increase 36
(nos. 3, 4, 6, 8, 9, 10, 11, 12, 17, 20, 21, 24, 25, 26, 28, 29, 31, 32, 34, 37, 39, 40, 44, 45, 52, 55, 57, 58, 60, 61, 62, 63, 68, 69, 70, 71)
Of these, 69 (800), 62 (850).
D. Chemistry, Paroxysmal Period (11 patients)
Dextrose: Hypoglycemia (nos. 13, 24 and 67) 3
E. Effect of Salt-Poor Diet on Chemistry (41 patients)
Dextrose: Hypoglycemia (29, 44, 57, 60) 4
Uric Acid: Increase (nos. 11, 21, 34, 36, 39, 51, 62, 68, 69 and 71) .. 10
Chlorides: General reduction
F. Wassermann Reaction (73 patients)
Positive (nos. 16, 41 and 73) 3

3. Renal Function
A. Phenolsulphonphthalein excretion (33 patients): Diminished 15
(nos. 3, 9, 12, 17, 20, 24, 27, 28, 29, 32, 45, 50, 52, 62 and 63)
B. The 24 Hour Urine (59 patients)
Albumin or casts (nos. 3, 7, 12, 13, 17, 32, 33, 54, 57 and 73) 10
C. Paroxysmal Urine (3 patients)
Albumin or casts (nos. 8, 10 and 27) 3
Dextrose (no. 27) 1
D. Fractional Urine Studies (30 patients)
Polyuria, nocturnal (nos. 4, 24, 26, 36, 38, 48, 60, 65, 68 and 70) 10
Fixation of specific gravity (nos. 34, 37, 51 and 54) 4
E. Effect of Salt-Poor Diet on Urine (54 patients)
General high chloride excretion lowered during course of diet

4. Sugar Tolerance (47 patients)
Glycosuria (nos. 1, 2, 16, 19, 21, 25, 26, 31, 35, 48, 52, 53, 60, 62 and 63) .. 15

5. Spinal Fluid (24 patients)
Positive Wassermann reaction (nos. 5, 16 and 54) 3
Paretic colloidal gold curve (no. 5) 1

6. Protein Sensitization (44 patients)
Food or bacterial 0
Homologous serum (epileptic) 0

7. The Sputum (61 patients)
Entirely negative by routine and biologic methods specified

8. The Feces (60 patients)
Constipated stools 23
Fluid feces 7
Gross blood (no. 64) 1
Poorly digested protein (nos. 22, 23, 49, 55, 57, 61 and 62) 7
More than 30 per cent gas after Schmidt diet (nos. 8 and 27) 2

9. Cardiac Function and Electrocardiographic Studies (58 patients)
Bradycardia (nos. 4, 5, 6, 9, 10, 20, 26, 27, 28, 30, 45, 60 and 61) 13
Mitral stenosis (no. 55) 1
Mitral insufficiency (nos. 31 and 40) 2
Bradycardia and sinus arhythmia (nos. 26 and 69) 2
Aortic dilatation (no. 18) 1

Neurocirculatory asthenia (nos. 36, 48 and 68) 3
Ventricular predominance (nos. 7, 13, 16, 31, 35, 44, 62 and 63) 8
Extrasystole (nos. 19 and 24) 2

10. Blood Pressure
Diurnal variations (29 patients): essentially physiologic
Postseizure variations (22 patients): increase in blood pressure proportional to the number and severity of the seizures and due to muscular exertion

11. Basal Metabolic Rate (36 patients)
High basal metabolic rate (nos. 3, 4, 35, 60, 61 and 62) 6
Averages well with control group

12. Roentgenographic Studies
A. Skull (60 patients) Including Only Well Recognized Abnormalities
Female type (nos. 11, 13 and 40) 3
Acromegalic type (nos. 9 and 65) 2
Brachiocephalic type (no. 12) 1
Dolichocephalic type (no. 60) 1
Syphilitic skull (nos. 3, 18 and 58) 3
Traumatic changes (nos. 5, 7, 13, 16, 20, 43, 57, 61, 67 and 70) 10
Increased intracranial pressure (nos. 7, 9, 10, 34, 57 and 62) 6
Calcification of pituitary gland (no. 25) 1
Pituitary tumor (no. 39) 1
Irregularity of internal table (nos. 47 and 52) 2
Irregularity of external table (no. 57) 1
Brain tumor (no. 62) 1
B. Thorax (55 patients)
Active or healed tuberculosis (nos. 13, 17, 27, 45, 48 and 61) 6
C. Thyroid Gland (35 patients): Enlargement (no. 26) 1
D. Thymus (35 patients): Persistent (no. 26) 1
E. Teeth (59 patients): Retained root or periapical abscess 30

13. The Sympathetic Nervous System
Vagotonic types (from 33 to 37 patients) 18
(nos. 5, 7, 13, 17, 20, 24, 25, 27, 29, 31, 32, 39, 40, 45, 47, 50, 63 and 68)
Sympatheticotonic types (47 patients)
(nos. 2, 6, 10, 11, 20, 21, 22, 24, 26, 31, 32, 34, 35, 36, 47, 50, 58, 60, 62, 65, 69 and 71) 22

CONCLUSION

An intensive laboratory study of seventy-three epileptic patients has been presented and the observations compared with the more limited investigations of other authors. The data reveal significant variations and suggest a more careful study of individual epileptic patients as a clue to the pathogenesis of epilepsy.

BRONCHIAL ASTHMA

THE SEVERE CHRONIC INTRACTABLE TYPE *

I. S. KAHN, M.D.
SAN ANTONIO, TEXAS

It is with considerable temerity that I bring up this subject, probably the most difficult and disheartening in the whole domain of allergy. Still, it is one that all workers in this field occasionally have to face. I am referring to the ill, disabled person with chronic asthma—the chronic daily user of epinephrine, often in heavy dosages and often over a period of several years, with occasional exacerbations requiring the hypodermic administration of morphine, often for several days at a time. Nasopharyngeal operations have been performed, vaccines, pollen extracts and nonspecific therapy of all sorts have been employed, and various changes of residence and dietary measures tried, all to only temporary, partial or no avail.

The patients are usually over 20 years of age, ordinarily poorly nourished and in miserable general condition. Loss of weight is considerable, and hypotension is the rule. Physical examination usually shows no pathologic process other than the persisting asthma with its accompanying bronchitis. Emphysema and changes in the chest wall are usually present. Laboratory tests do not reveal any unusual urinary or blood changes beyond secondary anemia. Eosinophilia, commonly accompanying allergic manifestations, is ordinarily not seen; in fact, in several counts on some of these persons in my practice, no eosinophils have been detected.

In diagnostic skin tests, by the ordinary dermal or intradermal methods, the reactions are usually either negative altogether or negative to the ultimately determined causal factors.

With the vast majority of cases of bronchial asthma at the present time on a demonstrable allergic basis, there seems to me no reason, beyond the previous failure to secure results under ordinary competent allergic management, for a different assumption in these difficult cases. The successful results ultimately secured in a number of these apparently hopeless incurable failures demonstrates the fact that many, if not all, of these cases are specifically allergic and not bacterial or reflex, whatever this term may signify, and that allergic measures carried out over a sufficient period of time will finally give the desired relief in at least a percentage of these instances.

* Submitted for publication, Jan. 7, 1930.

Negative reactions to skin tests, as has been demonstrated, do not bar the possibility of definite pollen or other specific etiology in bronchial asthma and other allergic conditions.

While most cases of seasonal hay-fever, with or without complicating asthma, clear up almost immediately with the cessation of the etiologic pollen season, such immediate recovery is not invariable. Often there is a delay of several days, even in the absence of any apparent coincident infection of the upper respiratory tract. In proved pollen-free rooms and with the use of pollen filters, definite cases of pollen hay-fever and asthma vary in the number of days required to obtain freedom from symptoms. This is also Cohen's [1] experience.

Granting previous approximately identical atmospheric antigen dosages, such differences can only be accounted for either by individual variations in the time required for the production of the necessary quantity of antibody needed for pollen toxin neutralization or by individual variations in the ability to excrete completely such toxin or toxins. Probably both factors are involved.

From a limited investigation of these slowly clearing cases, as stated previously, eosinophilia apparently is relatively not marked or is absent altogether. If one regards the eosinophil as the particular hematologic defensive, as well as the diagnostic, element in allergic conditions, this observation is significant. Not enough work, however, has been reported along this line for one to draw any definite conclusions.

I am advancing the theory that the absence of the expected positive skin reactions in these cases may be due to the failure of resistance, precisely analagous to the absence or disappearance of the previous positive Pirquet reaction in progressive advancing or acute tuberculosis.

The constant, daily, frequently repeated use of epinephrine may be advanced as another factor in the failure to elicit the usual cutaneous response to the causal antigens. But against this is the fact that in patients suffering acutely from hay-fever, the administration of this drug, to secure temporary relief, when followed even at once by the administration of pollen extracts intradermally, as originated by Phillips [2] for the coseasonal treatment for hay-fever, does not prevent or even delay the usual wheal and erythema reaction. So there is at least a possibility that negative skin reactions are due to a lack of antibody formation as well as a low degree of sensitivity, especially in early cases in young children, as reported last year.[3] This does not mean that

1. Cohen, Milton B.: Personal communication to the author.

2. Phillips, E. W.: Relief of Hay Fever by Intradermal Injections of Pollen Extract, J. A. M. A. **86**:182 (Jan. 16) 1926.

3. Kahn, I. S., and Grothaus, Emma M.: Incidence and Significance of Negative Skin Tests in Pollen Asthma in Infants and Young Children, J. Lab. & Clin. Med. **13**:949 (July) 1928.

frequently repeated daily doses of epinephrine may not account for the failure to elicit the usual cutaneous response in some of these cases.

The following case is typical of the unusual length of time required for the disappearance of symptoms following removal from antigen contact.

REPORT OF CASES

Case 1.—S. S., a banker, aged 52, who was first seen on Jan. 17, 1926, gave a history of steady and almost constant asthma for six months. Skin tests, given intradermally with 1 : 50 extracts, yielded slightly positive reactions to the grasses and very questionable ones to the ragweeds; otherwise the results were completely negative. Treatment was declined. The patient entered a hospital in San Antonio on Sept. 17, 1928, in a desperate condition, with a history of daily attacks of asthma for over a year, during which time he had increased his self-administered doses of epinephrine to 12 or 15 minims (0.74 or 0.92 cc.) every two or three hours. His condition became considerably worse with the onset of the ragweed season. Epinephrine was taken at times almost hourly, and occasionally with morphine or codeine, drugs to which he was later demonstrated to be nonsensitive. The onset and subsequent history in this case suggested a pollen etiology. The patient was considered too ill for retesting or for specific treatment. He was placed in a pollen-free room with a filter that was constantly in operation. Epinephrine and morphine were used as indicated, epinephrine being given almost hourly and morphine in one-fourth grain (0.016 Gm.) doses three or four times daily. He was desperately ill, requiring special attention day and night, delirious and on the verge of dying several times in the first forty-eight hours. Improvement started at the end of five days. He remained in the hospital for three weeks, at the end of which time narcotics were discontinued entirely and epinephrine was decreased to six doses daily. He then returned home to a neighboring city, where he remained constantly in bed behind a pollen filter until early in January, 1929. During this period there were two severe relapses, each of several days' duration, requiring an increase of morphine and epinephrine. No other drugs or medication, specific or otherwise, was used. The only break in the pollen-free environment was on the day when he was transported to his home from the hospital. Complete recovery for the first time in two years occurred on Dec. 29, 1928. Up to the present writing (Jan. 26, 1929), he has remained well and has not used epinephrine.

The interest in this case lies in the fact that in a ragweed-free room, as demonstrated by frequent pollen plates, complete freedom from symptoms did not occur until three and a half months after removal from all possible ragweed contact, or, if one considers the pollen filter as only partially efficacious, in spite of the failure of pollen plates to detect ragweed pollen, not until at least one and a half months after the last possible atmospheric contact with ragweed. It will be noted that the ragweed tests performed even two years previously gave practically negative results. I regret that no examinations of the blood were made in this case.

The permanent loss of a known original, definite, strong, positive skin reaction during the course of protracted severe asthma is a more conclusive proof of this conception of practically complete failure of allergy

antibody formation or its early exhaustion, and is illustrated by the following case:

CASE 2.—I W. B., a physician, aged 37, was first seen on July 2, 1928. The first attack of hay-fever occurred in May, 1927, in Mississippi. At this time he was tested by the dermal method. He gave huge positive reactions to grasses and ragweeds. His arm swelled badly and the hay-fever markedly increased. The first attack of asthma occurred in October, 1927, since which time (eighteen months) there had not been a single day of freedom and not a single night of unbroken sleep. From the start, epinephrine was required at least every three hours and frequently every hour. He was intolerant to morphine and its derivatives. The seasonable onset of his hay-fever and later his asthma obviously corroborated the pollen etiologic diagnosis. One month after the onset of the asthma the patient was tested by another allergist (Dr. Balyeat, of Oklahoma City)[4] and found to give positive reactions to house dust and feathers. The reactions to the pollen tests were so reduced in size only six months after the first attack of hay-fever as to be recorded as inconclusive or only slightly positive.

When he was first seen, this patient's condition was pitiable to an extreme degree. He was 72 inches (182.8 cm.) tall and weighed 109 pounds (49.4 Kg.), having lost 40 or 50 pounds (18 or 22 Kg.). His hair had turned completely gray, giving him an appearance at least twenty years older than his actual age. He could scarcely walk or stand. Pallor was marked, and the entire picture was that of advanced tuberculosis or carcinomatosis. However, the most searching repeated examinations, clinical, roentgenologic and laboratory, by myself and consulting internists, revealed nothing beyond a mild secondary anemia. Not a single eosinophil was encountered in a number of blood smears. Whether a previous extensive intranasal operation had anything to do with the loss of resistance in this case is, of course, purely conjectural. There was some intermittent nasal suppuration, not marked. The nasal mucosa, however, remained almost constantly in an uncontrollable state of typical allergic hypersensitiveness, with profuse watery discharge. This yielded slightly, and only temporarily, to ephedrine or cocaine derivatives. The paroxysms of asthma were severe and unbroken, except when the patient was under the influence of epinephrine.

The patient was placed in a pollen-free room, both home-made and commercial filters being made. Frequent plates showed this room free from pollen, fiber and dust, except on one or two occasions. The patient was a highly intelligent physician, who was thoroughly conversant with the literature on bronchial asthma and keenly on the lookout for nonspecific and specific antigens. All known antigenic foods were in turn removed from his diet, all to no avail. Though several periods of improvement and relapse followed, as is the rule in these cases, epinephrine was never reduced below three doses in twenty-four hours, even after a six months' sojourn in this environment. He was considered too ill for any considerable amount of testing. However, in November, dermal tests with both grasses and ragweeds gave absolutely negative results. Several recognized accidental introductions of ragweed pollen in his room, as proved by plates, were invariably followed by severe relapses which lasted a number of days. A thermometer was installed so as to permit the detection and correction of any wide variations in temperature. Feathers, animal hair, wool and odors were completely eliminated.

After six months of this routine, he recovered enough strength to be up for several hours daily, and real improvement seemed at last well on the way. Epinephrine

4. Balyeat, R. M.: Personal communication to the author.

was almost dispensed with. As the ragweed season had been over for a month, he was permitted to stop the operation of his filter to maintain more warmth. All went well for about ten days, when about December 25 with the onset of the winter mountain cedar pollination, a severe relapse ensued. It was then noticed that the patient in the adjoining room had had one of these pollinating trees installed as a Christmas decoration. Pollen plates in my patient's room were loaded with this pollen. He was then advised to leave San Antonio to go to Memphis, where at that time there was no atmospheric pollen. He was instructed to continue antigenic precautions. During the winter months there, epinephrine was reduced to four or five doses daily, with considerable improvement in his general condition. With the onset of the tree pollination season in Memphis, he relapsed again into his former state. Having no filter at that time, he was ordered to a densely settled portion of Chicago. Slow improvement again set in. However, in April, without advice, he took several 1:250,000 dilution doses of timothy pollen extract. This was followed by a decided relapse, which lasted until the present writing (May 27). When last observed, pollen plates showed his room to be pollen-free.

This case seems to me to represent an extreme degree of lack of antibody formation against pollen toxemia, combined with extreme pollen hypersensitiveness. In the light of present knowledge, specific or nonspecific therapeusis in my judgment was too risky to attempt. In my opinion, his only chance, as in all cases of this type lies in the hope that prolonged strict removal from antigen contact will ultimately lead to some natural restoration of the antipollen defensive mechanism, and render possible the subsequent exhibition of the usual specific methods of desensitization.[5]

It is conceded that I am unable by laboratory methods to advance any scientific proof either of this point of lack of antibody formation or of the inability to excrete allergic toxins, or for that matter, even of correct etiologic diagnosis. This article is merely the presentation of suggestive clinical cases. In not a single case of this series have I been able to secure positive reactions by the intradermal injection of undiluted blood serums into persons known to be very sensitive. In a similar manner, none has shown positive reactions by the passive transfer method.

To note the possibility of delayed excretion from the bronchial mucosa, a number of centrifugated sputum examinations were made following the close of the presumed etiologic pollen season, but the only pollen granules identified were those of the current pollen season. This, of course, does not preclude the possibility of alteration in pollen morphology by prolonged contact with bronchial mucus, making microscopic identification impossible.

5. As a further corroboration of this idea, as a result of the persistent continuance of antipollen precautions, by March, 1930, this patient was able to resume medical practice; eosinophilia (from 6 to 15 per cent) returned during rare light attacks, the original pollen skin tests were positive, and the patient was able to tolerate specific pollen treatment in comparatively high dosages.

The third possibility in connection with these cases, apparently borne out by repeated clinical observation, is that the failure to develop antibodies to their original antigenic factor renders them highly sensitive and nonresistant to numerous other known antigenic factors of no biologic relationship to the original excitant. In other words, other pollens, wool, feathers, cold air, foods and inhalant irritants can prolong the asthmatic state indefinitely for months or even years following the cessation of the pollination season in an original ragweed case, and often when no complicating infectious process is detectable. Frequently, patients who are not severely ill with asthma of ragweed etiology sooner or later develop sensitiveness, both cutaneous and clinical, to other pollens and also to these other antigens.

A word of warning should be mentioned regarding the use of the usual diagnostic skin tests in the cases of severe prolonged asthma. Immediate testing should not be done. Not only do such tests reveal negative reactions to later determined causal antigens, especially if pollen is a prime factor, but the futility of such testing seems complicated by the fact that there is frequently a high degree of systemic absorption from their employment. This was learned from bitter experience, when it was my custom to make a routine, thorough and complete test in every case of asthma. It was noted that a number of patients who showed immediate improvement in a pollen-free or completely antigen-free environment, giving every promise of total disappearance of symptoms within a few days, had relapses after such testing, especially with the pollens; the relapses were of marked severity, bordering in a few instances on a fatal outcome, and at times lasting for weeks. The conditions were such that only the tests could be incriminated. As an allergy worker, it was only with the greatest reluctance that I came to this conclusion. These untoward results have occurred especially when, after negative dermal reactions, negative reactions to 1:5,000 and 1:500 extracts used intradermally were followed by the use of 1:50 material. However, I have seen such relapses follow even the dermal tests or intradermal tests with 1:5,000 extracts.

Pollen tests, even by the intradermal method, can be made later with more safety, and few relapses, when the case has either cleared up completely or been kept under control by minimal dosages of epinephrine, provided such tests are made singly, infrequently and with carefully graduated extract strengths, when no setback from each previous dosage is noted. Even under such circumstances, positive reactions to skin tests are rarely securable, unless one considers diagnostically specific the constitutional relapse that occurs within twenty-four or forty-eight hours after the use of a pollen extract, intradermally or hypodermatically. These relapses often do not begin immediately after testing, the inception not occurring until twenty-four, forty-eight or seventy-two

hours later. Following the onset of the relapse, there is a steady increase in the severity of the symptoms for several days before a climax is reached. This climax is then maintained at times for weeks, clearing up only by a slow lysis which may cover another period of weeks.

If one is blocked by contraindicated diagnostic skin tests, how then is it possible to arrive at the etiologic factor or factors of these cases? A lengthy history is of immense value. Details are sought regarding the date and circumstances of the initial attack, the preceding bronchitis or hay-fever, seasonal exacerbations, the response in the form of improvement or relapses in various localities or places of residence, especially if seasonal, the effects of weather, winds, and drafts, sleeping indoors and outdoors, the effects of various kinds of pillows and known or suspected fiber, hair, dust and odor contact, aversion to various foods and drugs, and the presence or absence of urticarial or eczematous cutaneous manifestations.

Given a good working knowledge of the botany of hay-fever and of usual and unusual allergic antigenic factors, ordinarily without proceeding further a decidedly reasonable and not infrequently accurate presumptive etiologic diagnosis can be made, subsequently confirmed by environmental tests in the absence of securable laboratory confirmation. Even when its presence, previous or concurrent, is absolutely denied, it is remarkable in how many of these cases competent examination will show mild but definite typical allergic vasomotor rhinitis, frequently without other nasal disease; if such disease is present, it seems to be without any clinical bearing.

It is inconceivable to me that a nonresistant case of this type can remain one of single antigenic etiology. Also, it is immaterial whether animal hair or pollen was the initial originating excitant. These patients, as seen by the allergy worker, are practically invariably sensitive to both, also to dusts of all kinds, odors, drugs, even at times to morphine, but curiously enough, in my experience, seldom to foods.

On this assumption, these patients are placed behind pollen filters or in hotel rooms on a closed court; feathers, wool and all animal hair contacts are eliminated, rugs covered or removed, and every possible inhalant irritant eliminated. In other words, the environment is made dust, pollen and odor free, and meticulously kept so. Known antigenic foods, such as nuts, onion, honey, milk, eggs, wheat and cereals, are barred. All drugs, except epinephrine or ephedrine, are forbidden. This routine is maintained for weeks or even months if necessary, until recovery occurs, when subsequent specific desensitization can be carried out as indicated. Such specific desensitization should not be used until marked improvement, or preferably complete recovery, has been secured. Ordinarily I do not start such specific treatment until the case is at least down to two or three doses of epinephrine daily. I then begin

with extracts of 1 : 100,000 or even 1 : 500,000 dilution, repeated at first at weekly intervals, increasing very slowly and stopping at once with any temporary increase of symptoms. Ordinarily the symptoms of overdosage occur before the incidence of local reactions on the arm; in fact, even small erythematous local reactions are accompanied by severe prolonged relapses.

In presenting this subject, cases of asthma that clear up in this antigen-free environment within seven to ten days have not been considered. This discussion is limited to those cases that do not clear up or in which appreciable improvement is not secured under such conditions in this or even a much longer period of time. The possibility of overlooked or unrecognized antigens in an unknown percentage of these cases is readily admitted. Naturally, the more experienced and observant the allergy worker, the smaller is the number of cases that will fall into this category. Antigen overdosage from tests or specific overtreatment will account for some failures. Omission of called for treatment, specific or nonspecific, will account for others.

If, however, these patients can be persuaded to continue an indefinitely prolonged length of time under antigen-free conditions, freedom from symptoms in a certain admittedly relatively small percentage does occur. However, in several instances, I have seen from six to nine months of this routine required, with many interim severe protracted relapses of no demonstrable etiology.

I offer no apologies for a lack of statistics or for the admission of successful results in only a comparatively small percentage of these instances. Many of these patients drift away, owing either to lack of funds or to disappointment at not securing more prompt relief. Many instances of failure in allergic antibody formation are to be expected until knowledge of the mechanism required for its restitution is attained. Many patients die, after a few years of suffering, from exhaustion, cardiorenal disease or other complications.

To me it seems remarkable that any results can be secured in this type of case. The one ray of encouragement is that the relief secured in an estimated 10 per cent of my cases shows that by adhering to standard allergic methods of management, I am at least on the right track in handling all my cases of bronchial asthma no matter how stubborn or severe, and that the entity of intrinsic nonallergic asthma, as these cases would ordinarily be classified, is probably nonexistent.

The most discouraging feature of the type of cases I am describing is the extent of time, many weeks and even months, required to secure relief from symptoms, and the distressing number of frequently inexplicable explosive severe relapses before this relief is ultimately secured.

A somewhat similar state of relapse is seen in tuberculosis. It not infrequently happens that under strict rest in bed, the afternoon temperatures will gradually fall to normal. In spite of the strictest rest and even in the absence of complications, after a few days of such normal temperature there occurs a second rise of afternoon temperature lasting days or weeks and falling by slow lysis. Even a third or fourth repetition of this process will at times happen before a basic normal afternoon temperature is attained.

This long extent of time required for the clearing up of these cases of asthma, however, seems to me rather conclusive proof of the existence of a type of asthmatic subject who lacks ordinary resistance to allergic antigens, or who shows a markedly diminished ability to excrete their toxins.

CONCLUSIONS

1. There exists a type of asthmatic person in whom, even in the absence of other complications, antibody formation against allergic antigens or the allergen resistance factor, whatever that may be, is apparently greatly reduced or nonexistent, precisely as is the case analogously in tuberculosis and other bacterial infections.

2. In the absence of antigen reproduction, such as occurs in bacterial infections, there is probably combined with this lowered faculty of antibody formation a definite inability to excrete promptly the toxins elaborated by such allergic antigens following their complete withdrawal.

3. Eosinophilia is usually absent in these cases.

4. The usual diagnostic skin tests cause negative reactions, and if pollens are used, are dangerous.

5. In these cases there is gradual, and at times rapid, development of polyantigenic sensitiveness of high degree.

6. A small but appreciable percentage of these patients recover a certain amount of antibody formation and relief and even freedom from symptoms after many weeks or months of persistent elimination of antigenic contact without the institution of other therapeutic measures.

7. While there is no laboratory proof to support these contentions, the clinical results secured offer rather conclusive proof.

8. There exists no known reason why a patient should not fail to develop antibodies to allergic as well as to bacterial antigens.

ARTERIAL HYPERTENSION

EVALUATION OF THE PROGNOSIS *

EDWARD J. STIEGLITZ, M.D.
CHICAGO

A marked increase in the average mortality over the expected norm occurs in persons with arterial hypertension.[1] Great variations occur, however, and it is not without difficulty that the question of individual prognosis can be answered. The patient's inevitable query, "Will I get well? Can my blood pressure be reduced?" warrants careful attention. Large masses of statistics reveal merely the mean or average data, and all individual variations are ironed out. The patient is naturally not particularly interested in the average outlook for the group, but is vitally concerned in his own personal problem. The height of the arterial tension is wholly inadequate as a sole criterion of the prognosis;[2] the degree of diastolic hypertonia represents merely one of several factors which must be given due consideration.

Among the important factors affecting the prognosis in any specific clinical instance are: the age of the patient; the duration of the vascular disease; the etiologic factors involved; the degree of permanent, irreparable arteriolar sclerosis which has occurred; the association with other complicating disturbances such as cardiac or renal injury, diabetes or pregnancy, as well as the height of the diastolic arterial tension. As age increases, the life expectancy of course declines synchronously, but increasing age is not of great significance in altering the prognosis in hypertension. The average therapeutic response in patients from 60 to 70 years is as good as or better than that of younger patients.[3] The duration of the vascular disease is, however, a prominent factor in prognosis. The longer the duration of hyperpiesis, the greater the degree of arteriolar muscular exhaustion and replacement fibrosis or arteriolar sclerosis. Extensive arteriolar sclerosis being the end-point of the slow pathogenic progression, and being clearly an irreversible process, is of poor prognostic import. The arterial vessels may to some degree reveal the extent of such irreparable arterial changes,[4] but in certain

* Submitted for publication, Jan. 31, 1930.

1. Fahr, G.: Am. J. M. Sc. **175**:453 (April) 1928.

2. Post, W. E., and Stieglitz, E. J.: Am. J. M. Sc. **171**:648 (May) 1926.

3. Stieglitz, E. J.: Arterial Hypertension, Chapter VI. In press. New York, Paul B. Hoeber, Inc., 1930.

4. Agatston, S. A.: Fundus as Definite Index to Arterial Diseases with Analysis of 100 Cases, Arch. Int. Med. **42**:455 (Oct.) 1928.

instances this information may be misleading, as these vascular degenerative changes do not proceed at the same pace throughout the body.[5]

The significance of the etiologic background lies in the varying degree to which various factors are amenable to therapy. If hereditary predisposition to premature vascular degeneration is conspicuously manifest in the family history, it is of course of no avail to hope for any change in the intrinsic constitutional physiologic make-up of the individual patient. The influence of such heredity on vascular disease is irrevocable.[6] On the other hand, should specific infections such as dental sepsis or syphilis be regarded as significant, therapy may be expected to accomplish much. The same encouraging attitude may be taken with other etiologic factors such as dietary indiscretions, thyrotoxicosis and metallic poisoning. Typhoid fever in the past histories of patients with hypertension apparently affects the prognosis adversely.[7]

When extensive renal injury is found associated with arterial hypertension, the prognosis is definitely darker.[8] In part the greater hazard arises from the nephritis per se, in part from the anemia usually associated with chronic renal disease. The presence or absence of albumin or casts in the urine is not a sufficient criterion of renal injury, nor is the degree of albuminuria any index to the severity of the renal lesion. Severe renal failure may occur with no appreciable quantity of albumin in the urine. Severe renal disease occurs in only a small percentage of cases of hyperpiesis,[9] although mild renal injury is common. Of fundamental importance for proper recognition of the severity of the renal injury are functional studies, either with phenolsulphonphthalein, urea concentration, the Mosenthal test or more simply and with greater effectiveness with the concentration test.[10]

The greatest menace to life in hypertensive arterial disease is cardiac defeat or exhaustion.[1] It is important, therefore, to evaluate the status of the cardiac reserve. Estimation of the surplus of cardiac energy

5. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925; Arterial Lesions of Glomerulonephritis, ibid. **40**:80 (July) 1927.

6. Barach, J. H.: Constitutional Factors in Hypertensive Diseases, J. A. M. A. **91**:1511 (Nov. 17) 1928. Draper, G.; Allen, G., and Spock, J. C.: Studies in Human Constitution; Clinical Genetics, ibid. **92**:2149 (June 29) 1929.

7. Kalt, M.: Bull. Soc. d'ophth. **6**:309, 1928; Thayer: Bull. Johns Hopkins Hosp. **15**:313, 1904.

8. Addis, T.: Clinical Classification of Bright's Disease, J. A. M. A. **85**: 163 (July 18) 1925.

9. Paullin, J. E.; Bowcock, H. M., and Wood, R. H.: Am. Heart J. **2**:613 (Aug.) 1927.

10. Fishberg, A. M.: Unitary Nature of Impairment of Renal Function, Arch. Int. Med. **38**:259 (Aug.) 1926.

is not easy by specific tests.[11] Electrocardiographic studies of the heart in hypertension do not give particularly useful information unless an extensive myocardial degeneration has taken place, and they are then unnecessary.[12] Left ventricular preponderance is usually, although not invariably, present.[13] Organic valvular disease of the heart affects the prognosis adversely.[14] The most significant early signs of myocardial weakness are undue dypnea, undue tachycardia and cardiac consciousness or precordial distress occurring on exertion. The occurrence of these is best revealed by the patient's history.[15] Such signs of myocardial weakness make for a bad prognosis.[16]

Consideration of the factors mentioned which affect the prognosis in arterial hypertension emphasizes the complexity of the problem. However, the most important factor in the evaluation of the prognosis is the extent of permanent vascular injury. Hypertensive arterial disease is a slowly progressive process,[17] starting with increased arteriolar tonicity, with gradually appearing medial muscular hypertrophy,[18] and later, fatigue as the process continues. The muscular fatigue leads to increased muscular irritability, further spasticity and more fatigue. Thus a vicious circle is introduced which tends to perpetuate the process, although the original initiative irritating factors may have ceased to exist.[19] With further fatigue exhaustion occurs, and degeneration of the muscle fibers, with their gradual replacement by fibrous connective tissue, or arteriolar sclerosis appears. This fibrosis is not an invasive process, but a protective one to replace the exhausted and dead muscle cells. At this point the process becomes irreversible; prior to this stage, when the hypertension is due to muscular hypertonia, the process is relaxable, reversible and amenable to therapy. The pathogenic development from transient arteriolar spasticity to permanent collogenic scarring of the arteriolar walls is a slow, gradual, but

11. Baráth, E.: Ztschr. f. d. ges. exper. Med. **54**:58, 1927. Wallace, J. H.: Stair Climbing as a Test of Cardiac Function, Am. J. Dis. Child. **28**:282 (Sept.) 1924.

12. Ziskin, T.: Electrocardiogram in Hypertension, Arch. Int. Med. **42**:512 (Oct.) 1928.

13. Allan, G. A.: Heart **12**:181, 1926.

14. Cowan, J., and Fleming, G. B.: Quart. J. Med. **5**:309, 1912. Pitt, J. N.: Brit. M. J. **2**:118, 1887. Goodhart, J. J.: Lancet **1**:479, 1880.

15. MacKenzie, Sir James: Diseases of the Heart, ed. 4, Oxford, Oxford Med. Publications, 1925, p. 17.

16. Herrick, W. W.: Ann. Int. Med. **3**:467 (Nov.) 1929.

17. Stieglitz, E. J.: Arterial Hypertension, Chapter II, in press, New York, Paul B. Hoeber, Inc., 1930.

18. Hernohan, J. W.; Anderson, E. W., and Keith, N. M.: Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395 (Sept.) 1929.

19. Stieglitz, E. J.: J. Pharmacol. & Exper. Therap. **32**:23, 1927; **34**:407 (Dec.) 1928.

persistent evolution. The patient may be seen at any stage. Therefore to prognosticate properly it is of the utmost importance to determine the phase of development.

There are several criteria on which such identification may be based. The duration of the hypertension is an important factor. But the duration is unknown in the majority of instances, as hypertension is most asymptomatic in its early course and is frequently discovered accidentally. Persistence of diastolic hypertension is significant. If the diastolic pressure is maintained at 135 mm. or higher, the outlook for the patient is very dubious,[20] and renal impairment is to be expected.[21] Persistent diastolic hypertension is more significant than transient excessive hyperpiesis, as the degree of variability in the height of the diastolic tension constitutes an indirect but effective criterion of the extent of irrevocable arteriolar changes. In the presence of marked arteriolar sclerosis the peripheral resistance, as measured by the diastolic pressure, cannot vary greatly; it is relatively rigid or fixed, whereas with the purely functional spasticity of early vascular disease the arterial tension is characteristically fluctuant and variable. To determine whether the diastolic tension is or is not variable requires time and repeated observations, and the patient's justified demand is for a relatively immediate answer.

This information may be obtained in a very simple way. The soluble nitrites cause rapid and marked relaxation of the arterial tone and a corresponding fall in the blood pressure.[22] It has been pointed out [19] that as this vasodilator effect is so fleeting and transient, the soluble nitrites are of relatively little use in the therapy of arterial hypertension. For the purpose of observing the degree of relaxability of the arterial system, however, the soluble nitrites are invaluable. Amyl nitrite has proved most satisfactory because of its prompt efficiency in causing vascular relaxation, because it is so readily administered by inhalation from pearls and because the action is very brief. It is also useful as a gastro-intestnal antispasmodic [23] and in acute cerebral vasoconstriction.[24] Its effect on the pulmonary arteries is the same, though less marked, as on the systemtic vessels.[25] The vascular dilation and

20. Lian, C.; Broca, R., and Clément, J.: Presse méd. **29**:743, 1921.

21. Stieglitz, E. J.: Illinois M. J. **50**:234 (Sept.) 1926. Hamman, L.: W. Virginia M. J. **24**:157 (April) 1928.

22. Clendening, L.: Drugs, Modern Methods of Treatment, St. Louis, C. V. Mosby Company, Chap. II, 1924. Sajous: Analytic Cyclopedia of Practical Medicine, Philadelphia, F. A. Davis Company, 1915, p. 48.

23. Holmes and Dresser: Am. J. Roentgenol. **19**:44, 1928.

24. Frevez: Bull. et mém. Soc. nat. de chiv. **54**:238 (Feb.) 1928.

25. Love, G. R.: McGuigan, H., and Wiley, C. E.: J. Lab. & Clin. Med. **10**:885 (Aug.) 1925.

reduction of the blood pressure does not occur or is very slight in patients with extensive arteriolar sclerosis.[26]

The test is carried out as follows: After determination of the arterial tension, a pearl containing 5 minims (0.3 cc.) of amyl nitrite is broken, and the patient is asked to inhale deeply three or four times with the liquid held directly under the nose. As this is done, or immediately thereafter, the patient becomes very flushed and may perspire freely and complain of a sense of vertigo or impending syncope. It is at this time that the arterial tension is again determined, as at this moment the tension is at its lowest, the symptomatology being attributable to the acute vasorelaxation. During the period of flushing there is usually a tachycardia, sometimes, although not invariably, accompanied by cardiac consciousness or palpitation. The second observation of the blood pressure, at the minimum level, should be checked several times in rapid succession. After this the discomfort of the acute relative hypotension may be abbreviated by the administration of aromatic spirits of ammonia, either orally or by inhalation.

The response to this test in patients with arterial hypertension varies greatly. The degree with which the diastolic pressure approaches the normal level may be taken as a prognostic criterion of considerable moment, and also serves as an objective in therapy. The diastolic tension may fall below normal levels in early, purely spastic instances of hypertension, whereas in late cases with extensive fibrotic arteriolar changes, the fall may be relatively slight and it may be concluded that no therapeutic management can yield good results.

The accompanying tabulation of the results obtained with this procedure illustrates the type of response encountered, the interpretation given at the time and the therapeutic results obtained several months later. It is notable that in the forty cases cited, the prognostic interpretation was in gross error of the actual therapeutic results in only one instance (case AN 21). As with most clinical tests, the value depends to a great degree on the skill of interpretation. The table also illustrates the fact that age is unimportant as a criterion of the type of response to be expected. It is also manifest that the poorest type of response occurred in patients with reduced renal functional reserve. The author has found this procedure of great assistance in clinical practice. It is by no means finely accurate, nor does it pretend to give extensively detailed information. It has prognostic but no therapeutic use, and is purely a test to determine indirectly but physiologically the relaxability of the arterial system as a whole and thereby to evaluate approximately the extent of anatomic arteriolar damage. The same information is obtained by prolonged clinical observation, but the patient often justifiably demands a more immediate answer to his query.

26. Schert, D.: Wien. klin. Wchnschr. **40**:113 (Jan. 27) 1927.

The value and usefulness of this test may be further illustrated by a few more detailed specific case examples.

REPORT OF CASES

CASE AN 1.—*History.*—Mrs. R., 60 years old, a widow with one child was first seen on June 19, 1928, at which time an arterial tension of 210 systolic and 120 diastolic was observed. There was a strong hereditary factor in the etiology, as evidenced by four instances of apoplexy in the patient's family. The cardiac

Types of Response, Interpretation and Therapeutic Results of Procedure

AN No.	Sex*	Age	Vascular Tension Before Test	Vascular Tension After Amyl Nitrite	Percentage of Diastolic Return to Normal	Estimated Degree of Sclerosis	Prognosis Given at the Time	Time in Mo.	Vascular Tension Later (Results)	Comment
1	♀	60	210/120	130/ 80	100	0	Good	16	145/ 90	
2	♀	55	210/125	152/108	50	+	Fair	16	175/ 90	
3	♀	65	220/140	160/122	40	+++	Poor	2	.....	Died of cerebral hemorrhage
4	♀	57	220/116	122/ 70	100	0	Good	10	158/100	Died of gastric carcinoma
5	♀	57	180/114	140/ 96	60	+	Fair	12	160/110	Mild gout; low renal reserve
6	♀	59	215/145	160/120	30	+++	Poor	8	175/118	
7	♀	55	200/130	170/100	75	+	Fair	9	164/108	Syphilis
8	♀	60	220/108	170/106	0	++	Fair	5	176/106	
9	♀	67	198/110	142/110	0	+++	Poor	5	220/120	Low renal reserve
10	♀	64	178/112	158/102	50	++	Fair	24	160/ 90	Chronic arthritis
11	♀	72	210/ 90	110/ 50	100	0	Fair	16	180/ 80	Thyrotoxicosis with thyroidectomy (basal metabolic rate, 54)
13	♀	54	200/100	160/ 70	100	0	Good	14	150/ 90	Diabetes, myocarditis
14	♀	49	196/140	140/110	70	++	Poor	8	180/120	
15	♂	61	230/130	190/105	50	++	Poor	2	216/ 98	Low renal reserve; died of apoplexy
16	♀	36	160/102	134/ 84	100	0	Good	3	112/ 74	
17	♀	62	180/105	135/100	50	+	Fair	8	166/ 96	
18	♂	36	172/130	130/ 80	100	0	Good	8	144/ 90	Cervical rib with pressure
19	♀	48	190/130	130/105	50	++	Poor	10	190/105	
20	♀	48	180/115	140/ 95	80	+	Fair	8	150/ 96	
21	♀	65	184/106	148/100	40	++	Fair	7	210/110	Wrong prognosis
22	♀	50	200/110	170/105	20	++	Poor	2	190/110	
26	♂	39	180/110	128/ 78	100	0	Good	8	130/ 88	Past thyrotoxicosis
27	♂	36	220/140	170/120	40	++	Poor	3	215/145	Nephritis and anemia
28	♀	55	190/120	170/ 85	100	0	Good	4	152/ 98	
29	♀	49	230/120	170/120	0	+++	Poor	5	210/112	Died of cardiac failure
30	♀	52	240/140	150/100	80	+	Fair	4	196/110	
31	♀	35	180/132	130/ 76	100	0	Good	4	150/ 92	
33	♂	35	170/120	90/ 66	100	0	Good	6	118/ 72	Hypertension for 3 years
34	♀	74	230/100	180/ 95	50	+++	Poor	4	190/100	
35	♀	51	210/140	170/110	70	++	Poor	3	178/110	
36	♀	71	190/115	160/110	20	+++	Poor	13	180/110	Obesity
39	♀	29	190/118	140/100	65	++	Fair	11	175/110	Low renal reserve
40	♀	54	240/150	160/100	90	+	Good	3	155/ 90	
41	♀	39	206/125	164/118	35	+++	Poor	5	220/140	
42	♀	61	202/130	170/ 95	85	+	Fair	3	180/100	
43	♀	38	220/150	180/130	33	+++	Poor	25	240/160	Low renal reserve
44	♀	45	220/130	170/115	40	++	Poor	24	206/110	
45	♂	54	180/140	128/ 84	100	0	Good	3	140/ 80	
46	♂	56	152/105	110/ 78	100	0	Good	9	128/ 74	Cholecystitis with cholecystectomy
47	♀	46	160/103	130/ 88	100	0	Good	12	134/ 90	
48	♀	35	188/110	130/ 80	100	0	Good	8	126/ 75	Past eclampsia and severe nephritis
49	♀	59	245/120	215/120	0	+++	Poor	3	220/130	Retinitis, oral sepsis

* ♂ indicates male; ♀, female.

reserve was poor, with much dyspnea. Pregnancy had occurred when she was 40 years old, with marked intoxication. The renal reserve was reduced, the maximum specific gravity of the urine being but 1.018 after fourteen hours' deprivation of fluids.[10] On inhalation of amyl nitrite, the arterial tension fell to 130 systolic and 80 diastolic.

This marked fall in the diastolic pressure to a normal level indicated an absence of arterial muscular degeneration, and a good prognosis was offered despite the adverse factors of reduced cardiac and renal reserves. This interpretation given at the time was justified by the later course of events. On Dec. 21, 1929, eighteen months later, the arterial tension was 145 systolic and 90 diastolic, and the patient felt well. Therapy had been carried on with bismuth subnitrate.[19]

CASE AN 11.—*History.*—Mrs. S. F., aged 73, was first seen on Dec. 9, 1928, at which time the arterial tension was 210 systolic and 105 diastolic. Senility was manifest, with great emaciation and much fear. A coarse tremor was notable. Inhalation of amyl nitrite reduced the arterial tension at once to 110 systolic and 50 diastolic, a tremendous fall. Other than a distressing tachycardia, this violent reaction had no sequelae. Because of the emaciation, the tremor and relatively low diastolic tension, the basal metabolism was determined and found to be plus 54. In August, 1929, thyroidectomy was done after preparation with compound solution of iodine. In January, 1930, the last observations revealed an arterial tension of 170 systolic and 80 diastolic, a 25 pound (11.3 Kg.) gain in weight, and remarkable gain in vigor, considering the advanced age of the patient.

This instance illustrates that age alone is not an adequate criterion anent the amenability of arterial hypertension to treatment, and also that etiologic factors that may be removed, as thyrotoxicosis, affect the prognosis favorably.

CASE AN 15.—*History.*—P. G., a Greek, aged 61, was seen at the vascular disease clinic of Rush Medical College on March 3, 1929. He revealed a blood pressure of 255 systolic and 135 diastolic and a markedly reduced renal reserve. The maximum specific gravity of his urine reached only 1.016 on deprivation of water. On March 6, the amyl nitrite test was carried out. The arterial tension was 230 systolic and 130 diastolic before the test and fell to 190 systolic and 110 diastolic. Because of these data, a poor prognosis was offered. His arterial tension remained high, the lowest observed being 174 systolic and 112 diastolic on April 6. The patient died on May 30 following an apoplectic stroke.

CASE AN 33.—*History.*—J. E. V., aged 36, an industrial chemist, was first seen on Sept. 9, 1929. He stated that for three years he had known that he had hypertension, but that he was not certain concerning the blood pressure prior to that time. The arterial tension was 170 systolic and 120 diastolic. The basal metabolic rate was plus 10. An impairment of the renal reserve was moderate, the maximum specific gravity of the urine being 1.018 after deprivation of fluids[10] and the phenolsulphonphthalein secretion, 50 per cent in three hours. There was no anemia. On inhalation of amyl nitrite, the arterial tension fell from 170 systolic and 120 diastolic to 90 systolic and 60 diastolic. A question arose anent the reason for the reduced renal reserve: whether this was due to renal disease dating from a severe scarlet fever in childhood and aggravated by his daily exposure to fuming phenol, or whether the renal inefficiency was due to circulatory inadequacy because of the arteriolar spasticity. That the hypertension was due solely to spasticity was evident from the excellent vasorelaxation obtained with amyl nitrite. Therefore, a good prognosis was given.

On October 19, the arterial tension had fallen to 135 systolic and 88 diastolic and on October 21 to 140 systolic and 80 diastolic after treatment with bismuth subnitrite. On Jan. 14, 1930, the arterial tension was 118 systolic and 72 diastolic,

and the concentration test of the renal function revealed a satisfactory maximum specific gravity of 1.028. No bismuth subnitrate had been taken since Dec. 21, 1929. The improvement in renal function and the return to normal of the arterial tension confirmed the first prognostic impression, although at first glance and without the amyl nitrite test, the high diastolic tension and evident renal impairment suggested a poor prognosis.

The foregoing case histories serve to illustrate the usefulness of this procedure in evaluating the prognosis in arterial hypertension. In two of the instances cited (cases AN 11 and AN 33) the age of the patient, the high diastolic tension and evidence of renal impairment indicated extensive irrevocable damage, but the relaxability of the arterioles clearly demonstrated that the arteriolar hypertonia had not yet progressed to sclerotic degeneration, and that much could be expected from proper therapy.[19] Consideration of the physiologic mechanism of the peripheral circulation demonstrates that the logic of such a test procedure is sound.

No ill effects attributable to the inhalation of amyl nitrite in hypertension have been observed. The most marked sudden fall in arterial tension occurred in case AN 11, reported in detail. Nor is it felt that ill effects are at all likely to occur. The frequency with which amyl nitrite or nitroglycerol are administered with impunity in angina pectoris indicates strongly that the risk is minor if it exists at all. Therapeutically this procedure is valueless, as the vasorelaxation is far too transient to be of benefit; as an aid in evaluating the prognosis, however, it is most useful. Gradual, persistent and effective vascular relaxation is obtained with bismuth subnitrate.[19]

SUMMARY

The prognosis in individual instances of arterial hypertension should be based on several variable factors and does not necessarily coincide with the statistical average prognosis for groups of hypertensive persons. The factor of age is not of great moment. The factor of the etiologic background accounting for the hypertension is significant. Likewise are the status of the cardiac and of the renal reserve of importance. Most significant of all is the stage at which the vascular disease is encountered; whether the hypertension is of purely spastic origin or whether slight, moderate or extensive fibrotic changes have already taken place in the vessel walls. Spasticity and hypertonicity, no matter how severe, are amenable to therapy. Fibrotic scarring and replacement of degenerated muscle cells are not amenable to therapy, but represent permanent injury.

The degree of relaxability can be easily and rapidly determined by noting the response of the arterial tension to the inhalation of amyl nitrite. The type of response encountered has proved of great assis-

tance in properly evaluating the individual prognosis. In fifty instances, only one incorrect preliminary prognostic opinion was given. Relaxability of the arterioles is evidence of vascular disease relatively early in its pathogenic development, whereas the rigid fibrosed arteries of arteriolar sclerosis respond little or not at all. This procedure makes it easier to answer the patient's justified request for specific information relative to his outlook.

PLASMA PROTEINS*

H. J. WIENER, M.D.
AND
R. E. WIENER, PH.D.
NEW YORK

The source of the plasma proteins, the manner of their entry into the circulation, their life cycle as well as their physiologic functions still remain largely matters of speculation. Recent work on fibrinogen indicates the site of formation of this protein to be almost exclusively the liver.[1] The liver and the intestinal wall, as well as the blood-forming organs have been considered possible sites for the formation of the serum proteins. The liver, blood-forming organs and ductus thoracicus may be considered likely ports of entry of the proteins into the circulation. It must be conceded that any change in endothelial permeability may have an influence on the protein concentrations of the plasma. In how far the concentrations of the main fractions of the serum proteins and of the plasma fibrinogen reflect the cellular permeability of the organism as a whole or in part is speculative.

This communication deals with the determinations of the two main groups of the serum proteins, the albumin and globulin fractions, together with the plasma fibrinogen, cholesterol, calcium and some of the other blood constituents significant to the clinical condition studied. The pathologic conditions here reported include diabetes mellitus, benign glycosuria, localized and generalized infections, diseases of the liver and gallbladder, acute nephritis, chronic nephritis and nephrosis.

The proteins were separated by fractional precipitation of the plasma, and the nitrogen was determined by the Kjeldahl method and nesslerization. Magnesium sulphate was used for the precipitation of the globulin fraction and fibrinogen of the plasma, and the albumin was determined on this filtrate. The globulin was determined by the difference between the total serum protein determination on the defibrinated plasma and the albumin concentration. The plasma was defibrinated by coagulation through addition of calcium and separation of the fibrin in the clot.

The chemical method of fractional precipitation and determination of the separated fraction is the most reliable of the various methods. While the separation of the two groups of proteins by fractional pre-

* Submitted for publication, Dec. 11, 1929.

1. Howe, Paul E.: The Function of the Plasma Proteins, Physiol. Rev. **5**: 439, 1925.

cipitation is not chemically ideal, it does yield more reliable results than the other methods, especially in pathologic conditions, in which variations in other blood constitutents are apt to occur. If the concentration of the fraction is determined from a combination of refractometric and viscosity measurements of the serum, the influence of the lipoid fraction on the viscosity measurements will often cause an apparent increase in the globulin fraction. Furthermore, variations in the concentrations of other constituents not only may influence the viscosity measurements, but may cause an appreciable error in the refractive index measurement.[1] When a comparison between the total proteins of the serum, determined by refractometric measurement and the Kjeldhal method is made, it must be remembered that the factor of 6.25 by which the nitrogen determined is multiplied to give the protein represented does not equally apply to the two fractions. Nevertheless, the influence of other serum constituents may be seen in the variations of total protein determined by these two methods. The difference in the results as determined by the two methods may vary between 5 and 50 per cent in pathologic conditions.[2] The agents used for the fractionation of the two groups of proteins and whether the determinations were made on plasma or serum should always be stated. A certain time must necessarily elapse to allow clotting and retraction of clot, if serum is used. Resulting changes in acidity as well as enzymatic activities may result in changes in the protein concentration or in the relative concentrations of the fractions brought about by changes in their physicial properties or by stereoconfiguration changes.[3] The cholesterol was determined by a modified Bloor method and the calcium by a modification of the usual oxalate method.

The physiologic concentrations of the plasma proteins determined by the methods described on twenty healthy adults are given in table 1.

No difference between the sexes was found in the serum proteins, but a difference in the fibrinogen content of the plasma was noted. The variations in the plasma protein concentrations of the same subject during the year are slight; they tend to be greater in the female. The greatest variations occur during the menstrual period. The differences between the determinations made on the first day of menstrtuation and

2. Atchley, Dana, W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. M.: Physical and Chemical Studies of Human Blood Serum, Arch. Int. Med. **31**:606 (April) 1923.

3. Howe (footnote 1). Petschacher, L.: Spezifische Viscositatserhoehung und Kolloidzustand der Serum Eiweisskoerper, Ztschr. f. d. ges. exper. Med. **47**:325, 1925. Kimura, S.: Beitraege zur Kenntnis der Serum Protease. X Mitteilung. Ueber die Mehrheit der Serumprotease, nebst Bemerkungen zur Differenzieung und Charakterisierung der verschiedenen Serumproteasarten, Tohoku J. Exper. Med. **7**:561, 1926.

the eighth day in ten cases, calculated on the concentrations determined on the first day, averaged 8 per cent for the albumin fraction, 18 per cent for the globulin fraction and 14 per cent for the fibrinogen. The greatest variations found were: albumin, 15 per cent; globulin, 30 per cent and fibrinogen, 25 per cent. It is therefore prudent to avoid making determinations during this period. The serum protein concentrations during the course of five tests for sugar tolerance were also determined. The fluid intake in these tests was 500 cc. The variations in the total proteins as a rule were within 10 per cent; in only one case was an increase above that encountered (15 per cent). The patients in these cases were normal in respect to their protein concentrations. The average variation in the albumin was 10 per cent and that of the globulin fraction 20 per cent. It has been stated that variations due to food or fluid intake do not exceed 10 per cent.[4] Results of repeated analyses on healthy adults indicate that a plus or minus variation of 10

TABLE 1.—*Physiologic Concentrations of Plasma Proteins in Twenty Normal Adults*

	High, per Cent	Low, per Cent	Average, per Cent
Total serum protein	6.90	5.60	6.40
Serum albumin	5.00	4.20	4.60
Serum globulin	1.90	1.50	1.70
Plasma fibrinogen (male)	280 mg.	220 mg.	250 mg.
Plasma fibrinogen (female)	330 mg.	250 mg.	280 mg.
Albumin-globulin quotient	2.2 to 3.3, average 2.7		
Globulin-fibrinogen quotient (male)	5.2 to 7.6, average 6.8		
Globulin-fibrinogen quotient (female)	5 to 7, average 6.2		

per cent should be considered within the normal limits. All the analyses reported in this paper were made with the subject in a morning fasting condition, unless otherwise stated.

Table 2 shows the analyses of the proteins in fifteen cases of diabetes mellitus. The corpuscular volume, blood sugar and urine sugar at the time are also reported. The plasma cholesterol and plasma calcium were determined in fourteen of the cases.

The serum protein concentrations in uncomplicated cases of diabetes mellitus are within the normal limits. The albumin-globulin quotient is increased in cases 5, 8, 11 and 15. The high albumin-globulin quotients in case 5 (5.4 and 4.6) are due to an abnormally increased albumin with the globulin concentration reduced below the normal limit. This patient, extremely neurotic, had a tremor, and an increased pulse rate, but a normal basal metabolic rate. In case 8, the albumin-globulin quotient was 4; the albumin concentration was nor-

4. Adler, A.: Die physiologischen Schwankungen des Mischungsverhaeltnisses von Albumin und Globulin im menschlichen Blutserum, Deutsches Arch. f. klin. Med. **126**:61, 1918.

TABLE 2.—*Diabetes Mellitus*

Case	Date	Sex	Per Cent Serum			Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma			Globulin-Fibrinogen Quotient	Sugar		Comment
			Albumin	Globulin	Total Protein			Fibrinogen	Calcium	Cholesterol		Blood, Mg. per 100 Cc.	Urine at Time	
1	6/ 9/24	F	5.00	1.50	6.50	3.3	40.0	244	....	153	6.2	222	0	
	10/13/24		4.82	1.58	6.40	3.0	47.0	288	9.2	...	5.3	245	0	
	1/19/25		4.17	1.68	5.85	2.5	43.5	...	....	...	...	230	0	
2	5/ 6/24	F	4.56	2.12	6.68	2.2	....	...	9.6	...	...	200	0	
	2/ 1/25		4.35	1.67	6.02	2.6	48.5	371	....	...	4.5	226	0	
3	5/ 9/27	F	4.80	1.70	6.50	2.8	41.0	290	10.1	222	5.8	230	0	
4	4/27/27	M	4.31	1.81	6.12	2.4	36.5	263	....	170	6.9	170	0	
5	4/12/24	F	5.96	1.11	7.07	5.4	....	454	10.1	...	2.4	222	++++	On treatment with insulin; tremor; increased pulse rate; basal metabolic rate normal
	6/ 4/24		6.35	1.38	7.73	4.6	50.0	345	....	258	4.0	282	++++	
6	5/ 7/24	F	4.78	1.73	6.51	2.7	46.0	...	10.4	...	...	138	+/—	On insulin
	6/24/24		4.70	1.83	6.54	2.6	45.6	345	10.1	...	5.3	333	+++	2½ hours after lunch
	6/ 2/26		3.70	1.60	5.30	2.3	39.0	268	10.3	230	6.0	390	+++	2 hours after lunch
7	6/ 1/27	F	4.52	1.67	6.29	2.7	38.3	372	10.3	313	4.6	287	++++	3 hours after breakfast
8	3/31/27	F	4.33	1.09	5.42	4.0	36.3	338	10.5	214	3.2	325	+	Goiter; obesity; normal basal metabolic rate
9	6/ 9/24	F	5.22	2.45	7.67	2.2	37.7	455	9.7	228	5.4	182	+/—	Rheumatic pains
	5/23/26		5.06	1.55	6.61	3.2	....	330	....	280	4.7	333	+++	Feels well (2 hours after lunch)
10	11/22/26	M	3.93	1.78	5.74	2.2	40.7	330	9.6	412	5.4	147	0	
	4/23/27		4.05	2.13	6.18	1.9	36.8	340	9.2	420	6.3	204	0	Edema
11	5/18/25	M	4.80	1.05	5.85	4.6	35.6	412	10.6	175	2.5	156	+/—	Exophthalmos
12	4/21/26	F	5.90	2.82	8.72	2.1	....	...	12.0	200	...	154	0	Hypertension
13	7/ 7/24	F	5.64	1.58	7.22	3.6	37.5	...	9.8	...	...	125	0	
14	10/ 6/25	M	5.20	2.10	7.30	2.3	38.2	200	....	236	8.0	155	0	
15	1/27/27	M	6.38	0.92	7.30	7.0	45.0	262	9.3	244	3.5	90	0	Exophthalmic goiter
	3/14/24		3.80	2.28	6.08	1.7	36.8	300	....	170	7.6	119	0	Bronchitis, fever

mal, but the globulin concentration was decreased (1.09 per cent). This patient had a goiter but a normal basal metabolic rate. The patient in case 15 had exophthalmic goiter and glycosuria; the albumin-globulin quotient was 7 on his first visit. The albumin concentration was increased (6.38 per cent), and the globulin concentration was decreased (0.92 per cent). Six weeks later, during a period of acute infection of the respiratory tract, bronchitis with fever, the albumin concentration was 3.80 per cent, the globulin concentration was 2.28 per cent and the quotient was reduced to 1.7. Evidence of hyperglycemia later proved this case to be one of mild diabetes.

The influence of slight infections such as a cold or sore throat on the serum proteins may also be noted in cases 6 and 9. The patient in case 6 showed a decreased albumin concentration during a period of "cough and cold." In case 9 the globulin concentration decreased with the disappearance of signs of infection from a level of 2.45 per cent to a normal concentration.

Table 3 shows the analyses in six cases of benign glycosuria, some of which have been followed for a period of more than four years. Case 1 may be termed a borderline case in that the blood sugar, when the patient was not in a fasting condition, rose slightly above normal. The protein concentrations in all these cases were within the normal limits. The average concentrations were: albumin, 5.4 per cent and globulin, 1.64 per cent, the average quotient was 3.1. The average concentrations in the uncomplicated cases of diabetes mellitus were: albumin, 4.84 per cent; globulin, 1.74 per cent and the average quotient 2.8. There is practically no difference in the serum protein concentrations between the cases of "renal glycosuria" and the cases of diabetes mellitus. The plasma calcium concentration in the cases of renal glycosuria, just as in the majority of cases of uncomplicated diabetes mellitus, tends toward the high normal limit or is even slightly increased.

Table 4 gives the analyses in forty cases of either localized or generalized infections. Nineteen of the cases reported were cases of diabetes. The average protein concentrations in the diabetic cases were: albumin, 3.57 per cent; globulin, 2.68 per cent and fibrinogen, 620 mg. per hundred cubic centimeters. The same consistently lowered albumin concentration, increased fibrinogen and increase in the globulin concentration in the more severe cases is shown in the other cases uncomplicated by diabetes mellitus. The average concentrations in these cases were: albumin, 3 per cent; globulin, 3.17 per cent, and fibrinogen, 570 mg. per hundred cubic centimeters. The degree of variation from the normal in the two fractions of the serum proteins corresponds to the severity of the clinical condition. The progressive drop in the albumin-globulin quotient, mainly due to an increase in the globulin fraction, is well shown in cases 38, 39 and 40.

TABLE 3.—*Benign Glycosuria*

Case	Date	Sex	Per Cent Serum			Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma			Globulin-Fibrinogen Quotient	Sugar		Comment
			Albumin	Globulin	Total Protein			Fibrinogen	Calcium	Cholesterol		Blood, Mg. per 100 Cc.	Urine at Time	
1	1/ 8/25	F	4.60	1.90	6.40	2.4	44.0	436	9.3	256	4.4	138	4.3%	First day of menses (2 hours after breakfast)
	1/21/25		4.05	2.44	6.49	1.7	37.3	248	9.7	...	9.9	111	2.3%	Tonsillitis
	4/30/25		3.70	2.05	5.75	1.8	45.0	...	....	192	...	149	3.3%	Leukorrhea (not fasting)
	4/11/27		3.62	2.03	5.65	1.8	43.3	293	....	178	7.2	107	5.0%	
	4/25/27		4.30	1.76	6.06	2.4	38.0	269	....	...	6.5	105	4.2%	First day of menses
2	2/ 6/24	F	6.26	1.31	7.58	4.8	....	372	10.3	...	3.5	111	++	First day of menses; 3 hours after lunch; enlarged tonsils
	2/13/24		5.50	1.89	7.39	2.9	....	415	10.9	192	4.5	89	++	
	4/14/24		6.12	1.94	8.06	3.2	....	...	11.0	...	...	111	++	Not fasting
	4/28/24		5.22	1.94	7.16	2.7	43.0	...	10.5	...	...	100	1.7%	
	5/ 5/24		5.65	1.84	7.49	3.1	50.5	440	10.4	...	4.2	121	1.8%	Not fasting
	4/15/25		5.23	1.00	6.23	5.2	41.5	324	....	...	3.1	95	+++	
	3/28/27		4.50	1.38	5.88	3.2	38.1	247	....	167	5.6	105	1.7%	Tonsillectomy in September, 1926
3	5/ 1/25	M	5.80	1.60	7.40	3.6	46.5	...	....	133	...	133	++	Boy, aged 11; 2 hours after lunch
	5/29/25		4.83	1.91	6.74	2.5	47.0	...	10.7	170	...	93	++	
	12/21/26		3.90	1.00	4.90	3.9	46.0	156	....	85	6.4	106	2%	Extremely obese (3 hours after lunch)
	4/22/27		4.50	1.80	6.16	2.4	40.5	373	....	150	4.8	110	2%	Less obese (3 hours after lunch)
4	4/ 4/27	M	4.13	2.02	6.15	2.0	48.0	246	....	...	8.2	113	1.2%	3 hours after lunch
	4/15/27		4.50	1.62	6.12	2.8	44.5	253	....	150	6.4	100	1.5%	
5	5/18/25	M	4.60	1.90	6.50	2.4	49.2	269	10.1	...	7.0	104	+	
6	6/15/24	M	5.00	2.18	7.18	2.4	42.5	245	....	138	8.9	117	+	Not fasting

TABLE 4.—*Localized and Generalized Infections*

Case	Date	Sex	Per Cent Serum: Albumin	Per Cent Serum: Globulin	Per Cent Serum: Total Protein	Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma: Fibrinogen	Mg. per 100 Cc. Plasma: Cholesterol	Mg. per 100 Cc. Plasma: Calcium	Globulin-Fibrinogen Quotient	Mg. per 100 Cc. Blood: Non-protein Nitrogen	Mg. per 100 Cc. Blood: Uric Acid	Mg. per 100 Cc. Blood: Sugar	Comment
1	1/ 5/26	M	2.46	1.89	4.35	1.3	33.0	515	104	....	3.7	39	...	170	Gangrene; diabetes mellitus
	2/ 8/26		3.16	2.10	5.36	1.5	24.5	750	103	....	2.8	50	2.9	222	
2	1/15/26	M	3.85	2.15	6.00	1.8	33.0	435	167	....	4.8	..	...	170	Gangrene; diabetes mellitus
3	1/20/26	M	3.25	2.17	5.42	1.5	23.5	900	185	....	2.4	30	...	160	Gangrene; diabetes mellitus
4	2/15/26	M	2.76	2.76	5.52	1.0	22.0	780	144	....	3.6	..	...	250	Gangrene; diabetes mellitus
5	3/ 5/26	M	3.25	1.89	5.14	1.7	45.3	340	115	....	5.6	..	...	160	Gangrene; diabetes mellitus (post operation)
6	9/ 3/25	F	3.26	3.49	6.75	0.9	38.0	433	...	....	5.8	..	3.0	148	Gangrene; diabetes mellitus (ambulant clinic case)
7	2/ 8/27	F	2.19	2.31	4.50	1.0	19.3	550	130	....	4.2	38	4.2	116	Gangrene; diabetes mellitus (ambulant clinic case)
8	1/19/26	M	3.37	3.57	6.94	0.9	38.0	500	175	10.2	7.1	48	4.5	212	Appendicitis; diabetes mellitus
9	2/28/24	M	4.30	2.38	6.68	1.8	....	500	...	11.3	4.0	..	...	223	Infected toe; diabetes mellitus
10	7/28/27	F	3.00	2.38	5.38	1.3	39.4	578	76	....	4.1	21	...	230	Infected finger; diabetes mellitus; beginning erysipelas
	8/ 5/27		3.35	2.58	5.93	1.3	35.7	880	160	....	2.9	30	...	200	Has had two injections of erysipelas antitoxin; recovered
11	12/27/25	F	3.64	2.66	6.30	1.4	36.5	660	136	....	4.4	30	2.6	...	Infected hand (Staphylococcus aureus)
12	5/11/27	F	3.59	2.39	5.98	1.5	....	447	...	9.3	5.4	..	...	303	Ulcer of leg; diabetes mellitus
13	5/21/27	M	3.95	2.21	6.16	1.8	37.2	462	...	....	5.3	..	...	129	Furunculosis; diabetes mellitus
14	11/20/27	F	2.85	2.25	5.10	1.3	36.2	625	250	9.9	3.6	23	5.3	...	Temporal furuncle
15	1/ 6/27	F	2.37	2.59	4.96	0.9	15.6	600	304	9.1	4.3	130	...	...	Infection post curretage; anuria
16	4/14/27	F	4.90	2.84	7.74	1.7	36.0	568	...	....	5.0	..	...	190	Tuberculosis, pulmonary; diabetes mellitus
17	8/20/27	F	2.85	2.31	5.16	1.2	33.6	461	120	....	5.0	..	...	234	Pleurisy; diabetes mellitus
	8/30/27		2.46	3.24	5.70	0.8	30.0	565	146	....	5.7	..	...	400	
	7/15/29		4.25	1.81	6.06	2.4	36.1	197	150	....	9.2	25	...	285	No infection
18	8/ 8/27	F	3.69	2.54	6.23	1.5	36.0	650	94	9.6	3.9	29	...	...	Tuberculosis, pulmonary
19	7/15/27	F	2.71	3.89	6.60	0.7	41.6	900	...	....	4.3	..	...	...	Bronchitis
20	6/15/26	M	4.19	2.54	6.73	1.7	38.7	354	...	9.6	7.2	..	...	...	Tuberculosis, arrested pulmonary; icteric index 12
	11/ 5/27		3.75	2.10	5.83	1.8	45.6	278	288	9.5	7.4	40	...	...	Icteric index 12
	5/ 6/29		2.85	2.10	4.95	1.4	44.8	272	112	10.2	7.4	24	...	...	Icteric index 14
21	2/ 3/25	F	1.67	2.89	4.58	0.6	46.6	526	111	....	5.5	42	3.1	...	Infecticus asthma
22	2/ 8/26	F	3.74	2.30	6.04	1.6	35.8	625	163	....	3.7	40	1.0	...	Colitis; icteric index 8
23	2/13/26	M	2.70	2.36	5.06	1.1	19.6	422	98	10.5	5.7	52	5.7	...	Cystitis; prostatitis
24	8/16/27	M	2.81	2.06	4.87	1.4	32.9	923	267	....	2.2	25	...	183	Cystitis, postoperative for gangrene; diabetes mellitus
25	12/25/26	M	3.66	3.11	6.77	1.2	28.3	616	177	....	5.0	36	2.1	...	Cystitis; post suprapubic cystostomy
26	2/27/26	M	1.96	2.04	4.00	1.0	20.1	570	76	....	5.1	40	3.7	...	Cystitis; postoperative for bladder stone
27	3/ 1/26	M	2.32	3.63	5.98	0.6	31.0	643	85	....	4.0	56	4.4	...	Cystitis; prostatitis
28	3/ 8/26	F	2.94	2.88	5.82	1.0	22.7	715	142	9.2	3.3	33	4.1	...	Pyelitis

29	5/17/27	F	2.92	2.61	5.53	1.1	31.0	800	127	....	2.4	25	1.5	...	Pyelitis; five months pregnant
30	5/17/27	F	3.72	2.48	6.20	1.5	30.7	1,040	138	....	2.4	38	...	...	Pyelitis; five and a half months pregnant
31	3/14/27	M	3.45	2.08	5.53	1.7	....	322	180	9.4	6.4	25	...	...	Syphilis, tertiary; post recovery from arsphenamine jaundice
32	6/18/24	F	4.20	3.60	7.80	1.2	39.2	610	162	....	5.9	..	...	121	Syphilis, tertiary; diabetes mellitus
	6/11/26		5.24	3.85	8.89	1.4	32.0	625	230	....	5.9	..	...	122	
33	3/ 1/27	F	3.13	2.35	5.48	1.3	30.5	575	230	....	4.1	25	...	438	Syphilis, tertiary; diabetes mellitus
34	8/25/27	F	3.54	2.76	6.30	1.3	28.5	750	157	....	3.6	..	...	400	Syphilis, tertiary; diabetes mellitus; perforating ulcer
35	3/12/26	M	3.12	4.08	7.20	0.8	37.9	...	146	9.5	...	25	1.5	...	Syphilis, tertiary
36	2/ 5/29	F	4.36	3.06	7.41	1.4	42.3	416	104	9.6	7.4	25	...	...	Syphilis, tertiary
37	6/25/27	F	3.00	3.68	6.68	0.8	28.4	852	100	10.1	6.4	28	4.3	...	Pyelitis; five and a half months pregnant
38	12/22/24	F	2.58	1.43	4.01	1.8	....	371	268	....	3.8	28	3.9	...	Syphilis, tertiary; seven and a half months pregnant; chronic nephritis; hypertension
	1/25/25		2.87	1.88	4.75	1.5	24.5	657	...	....	2.9	31	6.1	...	Last of ten treatments with arsphenamine, Jan. 10
	1/30/25		3.38	3.05	6.43	1.1	33.6	800	335	8.8	3.8	46	7.3	...	Blood pressure 170/110
	2/16/25		3.78	3.78	7.56	1.0	35.0	636	...	9.0	5.7	43	5.0	...	Delivered of a living infant twelve days later
	3/26/25		2.75	2.90	4.65	1.0	30.0	702	193	8.8	4.2	54	5.9	...	Tubo-ovarian abscess
	5/11/25		2.44	3.26	5.70	0.8	24.4	577	99	....	3.0	40	6.1	...	High fever; colpotomy 4/21; transfusion 4/24
	6/ 8/25		2.03	4.47	6.50	0.5	23.3	630	153	12.4	7.0	40	6.1	...	Fever; cystitis; profuse vaginal discharge; blood pressure 130/90
	6/30/25		3.52	3.61	7.13	1.0	28.4	676	214	13.6	5.3	51	8.1	...	Cystitis; vaginal discharge; fever
	7/15/25		2.58	5.07	8.25	0.5	26.8	600	182	11.6	9.4	34	6.0	...	Cystitis; vaginal discharge; fever
	10/ 1/25		2.62	5.17	7.79	0.5	30.8	448	214	....	11.6	64	...	...	Cystitis and profuse vaginal discharge
	10/15/25		3.05	2.58	5.63	1.2	31.8	432	200	10.1	6.0	55	5.4	...	Blood pressure 150/112; creatinine (blood) 2 mg. per hundred cubic centimeters
	1/11/23		2.82	2.93	5.75	1.0	35.0	507	240	....	5.8	40	3.9	...	Increasing hypertension; blood pressure 170/105
	8/15/26		3.09	2.61	5.70	1.2	....	350	153	10.1	7.4	41	4.3	...	
	4/12/23		3.05	2.45	5.50	1.2	35.0	440	...	....	5.5	44	2.1	...	Blood pressure 190/135
	6/ 2/26		2.74	2.22	4.96	1.2	35.0	290	272	13.2	7.7	64	3.5	...	Blurred vision; blood pressure 190/136
	6/ 4/26		2.88	2.03	4.91	1.4	28.1	347	...	8.2	5.9	55	...	...	Died in pseudo-uremic coma
39	1/27/25	M	2.94	3.82	6.76	0.8	19.1	505	139	9.4	7.6	33	3.6	...	Acute leukemia; icteric index 6
	2/ 1/26		2.45	6.78	9.24	0.4	18.0	750	155	....	9.0	41	3.8	...	Icteric index 9; died ten days later
40	5/24/24	F	4.84	2.04	6.88	2.4	44.5	277	...	10.5	7.4	25	2.0	...	No complaints except slight tenderness in right hypochondrium region
	6/17/25		3.80	1.97	5.77	1.9	42.0	338	208	....	5.7	30	...	...	Chills; nausea; pain in right hypochondrium region; icteric index 13
	6/26/25		3.58	3.32	6.90	1.1	40.0	385	...	....	8.6	..	...	...	Agranulocytic angina, first symptoms 6/28; bilirubin 1.7 mg. per hundred cubic centimeters
	7/ 8/25		3.24	4.26	7.50	0.8	....	833	112	9.8	5.1	22	3.0	...	Direct van den Bergh positive; bilirubin 2 mg. per hundred cubic centimeters
	7/10/25		2.28	6.32	8.60	0.4	....	867	120	9.3	7.2	35	2.3	...	Icteric index 54; bilirubin 4.8; direct van den Bergh positive; died four days later

One patient (case 38), treated for syphilis and nephritis, was followed through a pregnancy and after delivery of a living infant, to death sixteen months later. The albumin-globulin quotient showed a decrease from the seventh month of pregnancy on, when syphilitic treatment was discontinued. The decrease in the quotient was mainly due to an increase in the globulin fraction, which gradually rose from a level of 1.43 to 3.78 per cent at term. The albumin fraction increased slightly during this time. The increase in fibrinogen was greater than that normally seen in pregnancy. A tubo-ovarian abscess developed four weeks after delivery. The patient ran an intermittent temperature, occasionally up to 104 F. Colpotomy was performed, and this was followed by a transfusion. The elevation in temperature continued intermittently for more than two months. The patient was discharged from the hospital three months after delivery, but cystitis and profuse vaginal discharge continued for more than four months. The albumin-globulin quotient decreased progressively after delivery (in February) and remained at an extremely low level until October. During this time the globulin concentration increased considerably, occasionally rising to a level of more than 5 per cent. During September and October the patient was given four treatments with neoarsphenamine, and her condition improved. The albumin-globulin quotient rose from a level of 0.5 to 1.2. At the beginning of June the following year she reported to the clinic with blurred vision, headaches and marked hypertension. Two days later pseudo-uremic convulsions and coma set in, and the patient died within twelve hours. The terminal azotemia was little increased beyond the limits observed in this patient before. There were no terminal changes in the serum protein concentrations.

Case 40 was a rapidly fatal case of agranulocytic angina. The first analysis shown (May 24, 1924) was made before the onset of the illness. In June of the following year the patient complained of abdominal pain and slight fever. Analysis of the blood on June 17 showed lowered albumin, increased globulin, increased fibrinogen, increased bilirubin and a slightly delayed, positive direct van den Bergh reaction. Nine days later (June 26) the globulin content of the serum had almost doubled. On June 28 the first symptoms of agranulocytic angina developed, ulceration of the mouth and a beginning leukopenia. The rise in the globulin continued, and fulminating sepsis with progressively increasing leukopenia led to her death seventeen days later. Four days before death the globulin concentration was 6.32 per cent.

The condition in case 39, acute leukemia, also presented the picture of a severe infection. The globulin, eleven days before the patient's death, rose to 6.78 per cent. The fibrinogen was 750 mg. per hundred cubic centimeters, and the albumin was materially decreased.

In infections showing clinical signs and symptoms the globulin is increased, and this increase seems to parallel the severity of the condition. The albumin is decreased, markedly so in the more severe conditions. The fibrinogen is increased and may show a decided increase in the milder conditions, which show no effect on the globulin concentration.

Table 5, analyses in twenty-three cases, shows the disturbed protein relationship in hepatic cirrhosis (twelve cases), cholecystitis (four cases), jaundice (four cases) and jaundice due to the use of Arsphenamine (three cases).

In these cases the parallelism between the severity of the condition and the decrease in the albumin-globulin quotient due to a decrease in albumin and an increase in globulin is also noted. The variations from the normal, however, are generally not so marked as those in the more severe infectious conditions shown in table 4.

In the cases of hepatic cirrhosis the changes in the fibrinogen concentrations as compared to the changes in the albumin and globulin concentration differ fundamentally from the observed changes in infectious conditions. In the infectious conditions, uncomplicated by a liver deficiency, the fibrinogen is always increased, the albumin is decreased and the globulin is increased in the more severe conditions only. In cirrhosis of the liver the albumin is decreased, the globulin is normal or moderately increased, but the fibrinogen remains within the normal limits or is even decreased below the normal concentration. In the infectious conditions the fibrinogen is always increased; in cirrhosis of the liver the fibrinogen will decrease with the progressive severity of the condition. The globulin increases while the fibrinogen remains within the normal limits or is even decreased.

The first analysis in case 8 shows the blood chemistry before the onset of clinical symptoms of hepatic cirrhosis. A moderate chronic sinusitis was responsible for the increased fibrinogen (402 mg. per hundred cubic centimeters) and cholesterol. The urine gave a two plus urobilinogen reaction, testifying to a slight liver insufficiency, and this may account for the relatively slight rise in the fibrinogen concentration in the presence of the infection. About nine months later, the patient complained of occasional intestinal disturbances with diarrhea. The blood chemistry at that time showed a greatly increased globulin concentration, while the fibrinogen was not materially increased and had actually decreased 10 per cent from the concentration found in the previous analysis. While the globulin had increased from 1.65 to 3.80 per cent, the fibrinogen had decreased from 402 to 360 mg. per hundred cubic centimeters. Three months later the blood chemistry revealed a decided decrease in both serum proteins, and the fibrinogen had decreased to a concentration below the normal, 214 mg. per hundred

TABLE 5.—*Diseases of the Liver and Gallbladder*

Case	Date	Sex	Per Cent Serum: Albumin	Per Cent Serum: Globulin	Per Cent Serum: Total Protein	Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma: Fibrinogen	Mg. per 100 Cc. Plasma: Cholesterol	Mg. per 100 Cc. Plasma: Calcium	Globulin-Fibrinogen Quotient	Mg. per 100 Cc. Blood: Uric Acid	Mg. per 100 Cc. Blood: Sugar	Mg. per 100 Cc. Blood: Non-protein Nitrogen	Icteric Index	Comment
1	12/15/26	F	2.82	3.53	6.35	0.8	....	300	238	....	11.8	1.0	133	22	38	Hepatic cirrhosis; acute alcoholism; died one week later
2	1/ 5/27	M	1.93	1.92	3.85	1.0	22.5	208	109	....	9.6	2.3	94	24	22	Hepatic cirrhosis; bilirubin, 4.8 mg. per hundred cubic centimeters; direct van den Bergh positive
3	2/ 1/27	M	2.94	2.46	5.40	1.2	43.0	186	...	....	13.2	...	106	35	7	Hepatic cirrhosis
4	1/10/27	M	2.65	4.89	7.54	0.5	40.0	274	223	....	17.7	4.3	...	..	14	Hepatic cirrhosis
5	5/19/27	M	3.58	2.48	6.06	1.5	....	340	192	....	7.3	...	...	..	6	Hepatic cirrhosis; not definitely diagnosed
6	7/20/27	M	3.45	3.10	6.55	1.1	40.0	472	143	....	6.6	6.0	109	33	..	Hepatic cirrhosis; alcoholism; syphilis
7	12/ 1/27	F	3.91	1.96	5.87	2.0	....	420	...	....	4.6	4.6	111	25	45	Hepatic cirrhosis; alcoholism
	12/ 4/27		3.65	2.85	6.50	1.3	36.3	450	91	....	6.2	2.4	...	..	50	Bilirubin, 5.3 mg. per hundred cubic centimeters; direct test positive
	12/14/27		3.96	2.74	5.70	1.1	33.6	348	233	....	7.9	3.3	98	30	20	Bilirubin, 2.5 mg. per hundred cubic centimeters; direct test very much delayed, positive
	12/21/27		3.14	2.40	5.54	1.3	28.3	300	244	....	8.0	1.7	89	35	6	Died three months later
8	12/ 9/26	M	4.20	1.65	5.85	2.6	41.6	402	223	11.2	4.1	3.7	...	27	..	Chronic mild sinusitis; hypertension; blood pressure 185/110
	10/27/27		4.30	3.80	7.10	1.2	37.5	360	138	....	10.1	4.0	...	29	..	Loose stools, 5 to 6 daily; stools negative
	1/30/28		3.33	1.15	4.48	3.0	40.5	214	167	9.9	5.4	4.6	...	30	6	Loose stools; loss of weight; blood pressure 150/80
	5/21/28		2.48	2.52	5.00	1.0	38.1	173	248	....	14.5	4.3	100	23	14	Loose stools; edema of ankles
	4/12/28		2.28	2.17	4.45	1.0	35.7	87	125	....	24.8	8.2	...	26	17	Stools again negative
	4/28/28		2.70	1.60	4.30	1.6	31.7	195	100	9.5	8.2	5.7	100	18	10	Small amount of fluid in abdomen; tapped 4/20; injection of emetine hydrochloride
	12/ 5/28		4.14	1.76	5.90	2.3	45.0	238	96	....	6.8	2.2	...	25	6	Exploratory 5/3; beginning hepatic cirrhosis; modified Talma operation
	5/16/29		3.45	1.25	4.70	2.7	50.0	279	121	....	4.5	3.3	...	..	6	Has gained weight and feels well
9	4/22/27	F	2.46	3.23	5.69	0.8	21.7	365	190	....	8.8	3.3	110	28	12	Hepatic cirrhosis; ascitis; Ur. urobilinogen +++
	5/19/27		2.45	2.25	4.70	1.1	21.2	430	223	9.4	5.2	...	151	25	12	Bilirubin, 0.4 mg. per hundred cubic centimeters; direct van den Bergh negative
	5/27/27		2.65	2.60	5.25	1.0	16.7	343	164	....	7.6	3.6	150	32	14	
	6/ 1/27		2.13	2.77	4.90	0.8	25.5	370	166	8.2	7.5	11.0	110	34	12	Transfused 5/27; chill after transfusion
	6/15/27		3.12	2.65	5.77	1.2	23.2	388	222	9.3	6.8	6.6	125	28	8	Bleeding from gums; platelet count, 160,000
	7/25/27		2.35	3.14	5.49	0.8	15.2	270	217	8.2	11.6	...	114	22	9	Platelet count, 7/5, 12,200; 7/13, 16,000
	8/11/27		2.95	2.80	5.75	1.0	16.5	191	156	8.5	14.8	7.5	...	26	8	Injections of horse serum; platelet count, 8/6, 310,000
	8/22/27		3.05	3.15	6.20	1.0	16.1	266	136	9.1	11.8	6.9	103	22	7	Injections of dextrose and insulin

	8/30/27		3.22	2.78	6.00	1.2	17.3	300	133	9.0	9.3	4.1	166	29	7	Ten units of insulin twice a day until 11/1/27
	9/10/27		3.45	2.61	6.08	1.3	17.6	282	125	9.6	9.2	5.7	133	28	..	Improving
	9/21/27		3.62	2.41	6.03	1.5	23.0	288	148	9.8	8.4	3.1	142	24	..	Still further improved
	11/ 2/27		4.18	1.57	5.75	2.6	22.5	295	208	9.6	6.2	4.6	90	26	..	Able to be up
	5/ 2/28		1.98	2.40	4.33	0.8	15.0	278	85	8.2	8.6	6.5	...	25	8	Progressive emaciation; ascitis; died 11/15/28
10	5/ 9/29	M	2.66	4.68	7.34	0.6	48.5	280	50	....	16.7	2.2	256	22	50	Hepatic cirrhosis; diabetes mellitus; pyorrhea; alcohol ++
	5/13/29		2.25	4.15	6.40	0.5	39.2	323	95	....	12.8	1.8	163	20	28	Bilirubin, 2 mg. per hundred cubic centimeters; slight edema; urobilinogen ++++
	5/16/29		2.41	3.87	6.28	0.6	35.8	334	91	....	11.7	...	382	..	29	
	5/27/29		3.29	3.99	7.19	0.8	39.5	418	80	....	9.6	...	382	..	29	Put on insulin; complains of fatigue; blood taken 2 hours after 50 carbohydrate, 5 protein, 10 fat
												...	322	..	22	Blood taken 2 hours after 50 carbohydrate, 5 protein, 10 fat
	5/31/29		3.90	3.02	6.92	1.3	....	380	90	....	8.0	...	259	31	16	Loose stools; blood taken 2 hours after 35 carbohydrate, 5 protein, 10 fat
	6/10/29		2.56	4.43	6.93	0.6	35.5	410	125	....	11.8	2.5	250	25	20	Nausea, vomiting and severe gastric distress; blood taken after food; patient put to bed
	6/13/29		3.04	3.24	6.28	0.9	41.3	368	172	9.0	8.8	...	138	..	17	Nausea; liver smaller
	6/22/29		2.73	2.97	5.70	0.9	33.5	379	153	....	7.8	...	107	27	14	Improved
	6/24/29		2.45	3.00	5.45	0.8	33.3	357	140	9.1	8.5	...	93	..	16	
	6/29/29		2.68	4.07	6.75	0.05	35.4	342	112	....	11.9	...	307	..	18	Blood taken after food; vomited 6/27, much gastric distress
	7/ 4/29		2.80	3.15	5.95	0.9	34.5	315	103	9.0	10.0	...	216	..	18	Feels much better; up and about; no edema
	7/16/29		2.40	3.45	5.85	0.7	34.9	247	130	8.9	13.9	...	314	21	14	Blood taken 1½ hours after carbohydrate 60; 7/12, three teeth extracted
	8/12/29		3.13	2.62	5.75	1.2	26.7	255	131	9.2	10.3	...	133	24	10	Feels much better and stronger
11	10/10/26	M	3.06	2.67	5.73	1.1	34.7	178	100	....	15.0	4.3	91	30	25	Hepatic cirrhosis (?); definite liver enlargement
12	2/10/26	M	2.78	2.72	7.50	1.0	38.9	184	...	....	11.0	3.0	...	25	..	Hepatic cirrhosis
13	1/11/27	F	3.72	2.58	6.30	1.4	35.0	392	...	....	6.0	...	...	..	43	Jaundice; slight fever; bilirubin, 6.2 mg. per hundred cubic centimeters; direct van den Bergh delayed
14	12/ 8/27	M	4.06	3.09	7.15	1.3	....	304	...	....	10.0	2.5	...	25	60	Jaundice; slight fever; urine urobilinogen ++++
	12/22/27		5.45	1.55	7.00	3.5	41.3	297	210	....	5.4	...	...	..	17	No visible jaundice; urobilinogen ++
	4/ 4/29		3.67	1.28	4.95	3.0	47.0	208	125	....	6.2	3.2	105	27	10	Urine urobilinogen +++
15	10/20/26	F	3.90	2.65	6.55	1.7	35.0	310	210	....	8.6	...	...	..	18	Jaundice; slight fever; bilirubin, 1.9 mg. per hundred cubic centimeters; direct van den Bergh negative
16	7/29/27	F	2.74	1.81	4.55	1.5	....	220	352	....	8.8	2.4	...	39	60	Jaundice; slight fever; bilirubin, 5.5 mg. per hundred cubic centimeters; direct van den Bergh positive
	8/11/27		3.52	3.61	7.13	1.0	43.2	238	330	....	15.2	...	...	..	20	
	8/16/27		2.96	2.80	5.75	1.1	37.4	300	274	....	9.3	2.0	...	29	19	
	8/26/27		3.26	1.40	4.65	2.3	41.5	310	261	....	4.5	...	...	..	10	
17	2/ 1/26	F	4.03	2.27	6.30	1.8	34.5	248	...	....	9.2	3.5	90	30	12	Cholelithiasis; bilirubin, 0.7 mg. per hundred cubic centimeters; direct van den Bergh delayed
18	7/28/27	F	3.80	2.30	6.10	1.6	....	400	120	....	5.8	...	95	26	20	Arsphenamine jaundice

TABLE 5.—*Diseases of the Liver and Gallbladder—(Continued)*

Case	Date	Sex	Per Cent Serum: Albumin	Globulin	Total Protein	Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma: Fibrinogen	Cholesterol	Calcium	Globulin-Fibrinogen Quotient	Mg. per 100 Cc. Blood: Uric Acid	Sugar	Non-protein Nitrogen	Icteric Index	Comment
19	2/15/27	M	3.76	2.52	6.28	1.6	34.0	440	...	....	5.7	...	100	30	33	Arsphenamine jaundice; gastric ulcer; bilirubin, 1.5 mg. per hundred cubic centimeters
	2/17/27		3.72	3.34	7.06	1.1	38.5	480	...	....	7.0	2.6	...	36	25	Bilirubin, 1.4 mg. per hundred cubic centimeters; direct van den Bergh delayed
	2/24/27		4.40	3.32	7.72	1.3	43.0	410	...	....	8.1	...	...	36	30	Bilirubin, 1.8 mg. per hundred cubic centimeters; direct van den Bergh delayed
	3/ 5/27		4.34	2.71	7.05	1.6	41.0	375	...	....	7.2	...	...	33	19	Bilirubin, 0.8 mg. per hundred cubic centimeters; direct van den Bergh negative
20	11/23/27	F	2.58	3.52	6.10	0.7	28.7	455	204	....	7.7	5.0	...	98	20	Arsphenamine poisoning; nephritis; pregnancy; direct van den Bergh delayed
	11/26/27		2.50	3.08	5.66	0.8	16.5	490	262	7.5	6.3	...	...	165	25	Bilirubin, 1.5 mg. per hundred cubic centimeters; direct van den Bergh slightly delayed; creatinine 6.8 mg. per hundred cubic centimeters
	11/27/27		2.95	3.40	6.35	0.9	20.0	630	290	8.3	5.4	17.3	...	160	27	Bilirubin, 1.7 mg. per hundred cubic centimeters; direct van den Bergh positive; creatinine, 6.8 mg. per hundred cubic centimeters
	11/30/27		2.09	3.51	5.60	0.6	19.0	513	298	8.5	6.9	16.6	...	190	25	Bilirubin, 1.7 mg. per hundred cubic centimeters; direct van den Bergh positive in 45 seconds; creatinine, 4.7 mg. per hundred cubic centimeters
	12/ 1/27		2.25	3.11	5.36	0.7	22.0	488	354	....	6.4	23.0	...	187	25	Bilirubin, 1.7 mg. per hundred cubic centimeters; direct van den Bergh positive in 30 seconds; creatinine, 3.0 mg. per hundred cubic centimeters
	12/ 3/27		2.67	5.04	7.11	0.5	23.0	596	453	9.0	8.5	9.2	...	175	27	Bilirubin, 2.1 mg. per hundred cubic centimeters; direct van den Bergh positive in 15 seconds; creatinine, 3.0 mg. per hundred cubic centimeters; died 12/7
21	12/22/26	F	3.65	2.60	6.25	1.4	....	735	...	....	3.8	...	182	..	80	Cholecystitis; diabetes mellitus; urine urobilinogen ++++; direct van den Bergh positive
	1/20/27		3.48	2.97	6.45	1.2	....	345	126	....	8.6	...	126	..	15	Bilirubin, 12/22, 7.5 mg. per hundred cubic centimeters; 1/20, 2.5 mg. per hundred cubic centimeters; direct van den Bergh negative
	5/15/27		6.20	3.00	9.20	2.1	....	550	...	....	5.4	...	143	..	6	Urobilinogen negative; direct van den Bergh negative
22	1/ 4/26	M	3.12	1.96	5.08	1.6	43.2	1,130	...	....	1.7	3.6	133	37	25	Cholecystitis; cholelithiasis; direct van den Bergh delayed
	1/21/26		5.50	5.96	11.48	0.9	36.0	1,500	...	....	3.9	3.2	143	25	5	One day after operation
	2/ 1/26		3.38	2.10	5.48	1.5	35.2	513	...	....	4.1	4.9	150	36	12	
	3/10/26		2.22	2.60	4.82	0.9	44.7	370	173	....	7.0	...	173	47	20	Bilirubin, 2 mg. per hundred cubic centimeters; direct van den Bergh negative; glycosuria
23	11/21/27	F	4.44	2.89	7.33	1.5	...	963	...	....	3.0	...	...	..	33	Cholecystitis; bilirubin, 1.5 mg. per hundred cubic centimeters; direct van den Bergh positive

cubic centimeters. Physical examination in February showed the upper border of the liver in normal position and the lower border just palpable on deep inspiration only. The urine showed a trace of bile and urobilinogen two plus. Increased intestinal action with loose stools continued, and toward the end of March there was occasionally edema of the ankles. On March 21, the liver was not manifestly enlarged, the spleen was not felt and there was no manifest free fluid in the abdominal cavity. The urine gave a four plus urobilinogen reaction, but in all other respects was normal. The feces on repeated examination were normal. The blood chemistry showed a further decrease in the albumin concentration (2.48 per cent), and the globulin fraction had increased (2.52 per cent). The fibrinogen was still further decreased, 173 mg. per hundred cubic centimeters. X-ray visualization of the gallbladder with the dye test failed; the gastro-intestinal x-ray series were also negative. On April 21, there was fulness in the abdomen which was tapped. The fluid withdrawn showed the characteristics of a transudate. The test meal showed an absence of free hydrochloric acid. The Wassermann test was twice found negative. On April 12, the albumin was 2.28 per cent, the globulin was 2.17 per cent and the fibrinogen had reached the low level of 87 mg. per hundred cubic centimeters. Injections of emetine hydrochloride were started on April 21 and injections of a bismuth compound on April 29. The blood chemistry on April 29 showed a slight improvement, albumin 2.71 per cent, globulin 1.60 per cent and fibrinogen 195 mg. per hundred cubic centimeters. An exploratory operation was performed on May 3. There were then several liters of fluid in the abdominal cavity. The liver was slightly enlarged, was hard and had a granular surface. Microscopic examination of a small piece removed showed beginning portal cirrhosis. A modified Talma operation was done. The patient since discharge from the hospital has gained weight, feels well and has been attending to his professional duties. In December of the same year his serum protein concentrations were normal, the albumin-globulin quotient was 2.3, and the fibrinogen concentration was 238 mg. per hundred cubic centimeters. In May, 1929, the serum proteins while slightly below normal gave an albumin-globulin quotient of 2.7, and the fibrinogen had risen to 279 mg. per hundred cubic centimeters.

Case 9 was followed for a period of seventeen months. When first seen the liver was markedly enlarged, and the spleen was moderately enlarged. There were subicteric sclerae and emaciation. The urine gave a four plus urobilinogen reaction. On the first analysis the albumin was 2.46 per cent, the globulin 3.23 per cent and the fibrinogen 365 mg. per hundred cubic centimeters. On rest in bed the albumin-globulin quotient improved somewhat, due to a decrease in the globulin concentration. The fibrinogen rose to 430 mg. per hundred cubic centi-

meters. This is the highest fibrinogen concentration found during the course of this illness, which ended in death seventeen months later. During a time of considerable prostration and bleeding from the gums, the fibrinogen was reduced to 191 mg. per hundred cubic centimeters while the globulin was increased above the normal concentration. The patient was given injections of dextrose and insulin and afterward insulin treatment, 10 units twice daily. There was considerable transient improvement, so that she was able to leave the city for the seashore toward the end of the summer. This improvement was accompanied by a slight rise in the albumin and fibrinogen concentration and a fall in the globulin concentration. In the late fall she was still further improved. At that time the albumin was 4.18 per cent, the globulin 1.57 per cent and the fibrinogen 265 mg. per hundred cubic centimeters, i. e., below the normal. In January the following year ascitis developed, which necessitated increasingly frequent tapping from then on. The decline was gradual, interrupted by slight transient improvements. On May 2 the globulin had again risen to 2.4 per cent with a fibrinogen slightly below the normal limit. The albumin had decreased to 1.98 per cent. The tendency to bleeding was then being controlled by injections of fibrogen. The patient died six months later.

The changed relationship between fibrinogen on the one hand and albumin and globulin on the other is also shown in case 10, that of a man, aged 52 years, with hepatic cirrhosis, diabetes mellitus and dental abscesses. The influence of a concurrent infection on the fibrinogen and globulin concentrations is well illustrated by this case. The dental infection was severe, three of the teeth being abscessed. The albumin at the time of the first visit was 2.66 per cent, the globulin 4.68 per cent and the fibrinogen concentration within the normal limits, 280 mg. per hundred cubic centimeters. Rest in bed and treatment with insulin for the diabetes mellitus brought about clinical improvement. The hypertension found on the first visit decreased, and the liver decreased in size. The globulin concentration gradually was lowered to 3 per cent, while the fibrinogen increased to 380 mg. per hundred cubic centimeters. The blood chemistry during this time reflected the clinical condition. An acute intestinal upset promptly caused a rise in the globulin to as high as 4.43 per cent. Four days following the extraction of the infected teeth, while the healing process of the gums was not complete, there was a drop in the fibrinogen (247 mg. per hundred cubic centimeters), while the globulin had slightly increased (from 3.15 to 3.45 per cent). Four weeks later, when the gums had completely healed, the globulin was 2.62 per cent, the albumin had increased to 3.13 per cent (from 2.40 per cent) and the fibrinogen was 255 mg. per hundred cubic centimeters. This case illustrates the inability of the diseased liver to respond to the

irritation caused by an infection as expressed by the fibrinogen concentration. The fibrinogen failed to rise proportionately, while the rise in the globulin exceeded that expected from the nature of the infection.

The average protein concentrations in the first nine cases of hepatic cirrhosis were: albumin, 3.15 per cent; globulin, 2.57 per cent; fibrinogen (male), 254 mg. per hundred cubic centimeters; (female), 324 mg. per hundred cubic centimeters. The average protein concentrations in case 10 while the infection persisted were: albumin, 2.55 per cent; globulin, 3.40 per cent and fibrinogen (male) 319 mg. per hundred cubic centimenters.

The five cases of jaundice without elevation of temperature (12—16) had a total protein concentration approaching the high normal limit. The albumin fraction was slightly decreased and the globulin fraction was somewhat increased. The average albumin-globulin quotient in these cases was 1.6. The fibrinogen was normal or slightly increased. In case 16 the patient had a decided jaundice on her first visit (icteric index 60, direct van den Bergh positive in one minute, bilirubin by indirect method 5.5 mg. per cent). The jaundice gradually subsided, and fourteen days later the icteric index was 20. The blood chemistry on the first analysis showed a greatly reduced albumin concentration, (2.74 per cent), normal globulin and reduced fibrinogen (220 mg. per hundred cubic centimeters). On her second visit the albumin had increased to 3.53 per cent, the globulin had more than doubled (3.61 per cent), while the fibrinogen remained practically the same. Five days later the total protein concentration was found to be 5.75 per cent, and the fibrinogen had increased to normal concentration. As the jaundice cleared up, the albumin-globulin quotient returned to normal, though the serum proteins were below the normal concentration, especially the albumin fraction. In case 14 the same phenomenon of an increase in the globulin concentration shortly after the jaundice developed with a return to normal as the jaundice cleared up, is to be observed. This was a case of consistent urobilinogenuria, and the decline in the total serum protein concentration as well as in the fibrinogen concentration found sixteen months later would indicate an increase in the liver insufficiency.

The insufficient response to an infection by the liver as expressed by the fibrinogen concentration is also shown in the cases of jaundice due to the use of arsphenamine and the case of arsphenamine poisoning. In the two cases of jaundice due to the use of arsphenamine the fibrinogen was below the level usually found in syphilis. In case 20 is reported rapidly fatal arsphenamine poisoning during pregnancy, complicated by nephritis. The fibrinogen was not increased beyond the limits usually found during the later months of a normal pregnancy. The albumin-globulin quotient on the day of admittance was 0.7, owing

to a much decreased albumin and increased globulin. The quotient decreased to 0.5, and the globulin rose from 3.52 on the day of admission to 5.04 per cent.

In case 21, that of a woman with mild diabetes and a definite cholecystitis, the fibrinogen was markedly increased, the albumin was decreased and the globulin was above the normal limit. The bilirubin was 7.5 mg. per hundred cubic centimeters, and the direct van den Bergh reaction was positive. The urine showed a three plus urobilinogen reaction. Five months later, when the patient had completely recovered from the jaundice, the serum proteins were much increased with a normal albumin-globulin quotient. The patient in case 22, an operative case of cholelithiasis and cholecystitis, showed this transient rise in the serum proteins, intensified by the effects of the anesthesia, in an exaggerated form. Two weeks before the operation the blood chemistry showed a decreased albumin concentration, high normal globulin and a much increased fibrinogen concentration (11.30 mg. per hundred cubic centimeters). The day following the operation the serum proteins were 11.48 per cent (albumin 5.50 per cent, globulin 5.96 per cent), and the fibrinogen had increased to 1,500 mg. per hundred cubic centimeters. Ten days later the analysis gave normal total protein with the albumin fraction slightly below normal and the globulin somewhat increased. The albumin-globulin quotient was 1.5. The fibrinogen was 513 mg. per hundred cubic centimeters. Seven weeks later, after the patient had left the hospital, the icteric index had again risen to 20, glycosuria had developed and the total proteins were reduced below the low normal limit. There was a further decrease in the albumin fraction, while the globulin had risen to 2.60 per cent. The fibrinogen was 370 mg. per hundred cubic centimeters. This unfavorable analysis was reflected by the clincal condition.

Number 1 in table 6 is a case of myelogenous leukemia in a woman, aged 47, who was under treatment for two and a half years. At her first visit the white blood cell count was 238,000. The globulin was 3.36 per cent, the albumin was 2.44 per cent and the fibrinogen was at the low normal level (286 mg. per hundred cubic centimeters). Roentgen treatment was started, and about one year after the patient's first visit the globulin was 2.38 per cent, the albumin was 4.40 per cent and the albumin-globulin quotient was 1.9. The fibrinogen had increased to 489 mg. per hundred cubic centimeters. During a period of leukopenia brought on by roentgen treatments, the albumin fraction and the fibrinogen decreased, while the globulin remained stationary.

The analyses in a case of pernicious anemia are given in case 2. The abnormally low globulin concentration found by Erben [5] in this

5. Erben, F.: Die chemische Zusammensetzung des Blutes bei pernicioeser Anaemie, Ztschr. f. klin. Med. **40**:266, 1900.

TABLE 6.—*Miscellaneous Conditions*

Case	Date	Sex	Per Cent Serum			Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma			Globulin Fibrinogen Quotient	Mg. per 100 Cc. Blood		Comment
			Albumin	Globulin	Total Protein			Fibrinogen	Cholesterol	Calcium		Nonprotein Nitrogen	Uric Acid	
1	3/ 1/26	F	2.44	3.36	5.80	0.7	....	283	119	11.6	11.7	30	4.6	Myelogenous leukemia; white blood cells, 238,000
	2/11/27		4.40	2.38	6.75	1.9	33.2	480	230	9.6	4.9	31	...	Roentgen treatment since 3/21/26
	5/21/27		3.40	2.45	5.85	1.4	....	283	110	8.7	8.6	24	...	Leukopenia; white blood cells, 650; no x-rays since April; died, spring, 1929
2	1/20/26	M	4.11	1.50	5.61	2.7	10.0	300	120	9.2	5.0	35	3.3	Pernicious anemia; blood sugar, 147 mg. per hundred cubic centimeters; chlorine as sodium chloride; plasma, 644 mg. per hundred cubic centimeters
	2/ 1/26		5.60	0.50	5.80	20.0	10.5	109	135	8.4	5.2	36	5.2	Died week later; icteric index, 9; chlorine as sodium chloride; plasma, 635 mg. per hundred cubic centimeters
3	3/27/29	F	3.92	2.08	6.00	1.9	35.7	250	120	....	8.4	22	...	Pernicious anemia, very early stage, severe cystitis; icteric index, 22
4	12/ 7/28	M	3.05	2.78	5.83	1.1	20.0	122	97	....	22.8	24	...	Chronic benzene poisoning, bleeding, leukopenia, anemia
	12/13/28		....	....	5.81	...	21.1	315	68	....	....	..	3.5	Transfused
	1/10/29		4.03	2.03	6.06	2.0	26.8	330	135	8.8	6.1	..	...	Transfused
	1/22/29		3.13	2.10	5.23	1.5	26.3	291	125	9.8	7.2	..	...	
	2/ 1/29		3.79	2.39	6.18	1.6	....	333	115	....	7.2	..	...	Discharged January 31
	2/11/29		3.30	2.40	5.70	1.4	28.0	271	119	....	8.8	..	...	
	4/ 1/29		3.30	1.74	5.04	1.9	35.1	244	119	....	7.1	..	...	Feels well
5	4/ 1/29	M	3.05	1.30	4.35	2.3	33.7	254	90	....	5.1	..	...	Chronic benzene poisoning, slight; ambulant case
6	2/14/26	F	3.77	3.65	7.42	1.0	....	....	....	....	....	17	...	Pemphigus (serum analysis)
7	2/14/26	F	4.10	3.73	7.83	1.1	....	....	....	....	....	..	...	Pemphigus (serum analysis)
8	9/21/27	F	2.98	3.24	6.22	0.9	40.8	520	172	10.4	6.2	33	2.0	Pemphigus
9	9/16/28	F	3.61	3.04	6.65	1.2	35.8	440	235	10.2	6.9	25	1.6	Xanthoma; diabetes mellitus; blood sugar 488 mg. per hundred cubic centimeters (not fasting)
10	11/12/25	M	4.30	3.30	7.60	1.3	46.2	570	156	11.4	5.8	..	...	Xanthoma; diabetes mellitus; blood sugar, 190 mg. per hundred cubic centimeters
	11/23/26		3.66	2.28	5.93	1.6	49.0	370	209	11.2	6.1	25	5.2	Insulin treatment; blood sugar, 210 mg. per hundred cubic centimeters
	12/30/26		4.13	2.49	6.62	1.7	41.3	550	234	....	4.5	..	...	One and a quarter hours after carbohydrate 68, protein 45, fat 68, blood sugar 256 mg. per hundred cubic centimeters
	1/18/27		5.05	2.87	7.92	1.8	48.0	500	139	....	3.7	..	3.7	Blood sugar, 178 mg. per hundred cubic centimeters

condition is present. In case 3, a case of early pernicious anemia, the globulin was 2.08 per cent. This relatively high concentration was due to a severe cystitis. The concurrent infection, however, did not affect the fibrinogen concentration, which was at the low normal limit. The icteric index was 22, and the urine gave a two plus urobilinogen reaction.

Cases 4 and 5 are of chronic benzol poisoning. The patient in case 4 on admission had an albumin-globulin quotient of 1.1. The globulin was increased and the fibrinogen markedly decreased, 122 mg. per hundred cubic centimeters. Tendency to bleeding and purpuric spots were present. With improvement in the clinical condition, the fibrinogen rose to 315 mg. per hundred cubic centimeters and maintained a high normal level from then on. Case 5 was a mild, ambulant case, in a man exposed to benzine fumes. The serum proteins were decreased, but the albumin-globulin quotient was normal.

These four cases resemble in the relationship between globulin and fibrinogen concentrations the cases of liver insufficiency shown in table 5. The next four cases in table 6 (6 to 10) resemble the infectious conditions in their protein concentrations.

Cases 6, 7 and 8, are cases of pemphigus. The albumin was moderately reduced and the globulin markedly increased. The fibrinogen was determined in one instance only and was found to be increased. The other two analyses were made on blood serum. The blister fluid was analyzed in case 6, and the protein concentrations practically checked the determinations made on the blood serum. The serum albumin was 3.77 per cent; in the blister fluid the albumin was 3.62 per cent. The serum globulin was 3.65 per cent; in the blister fluid the globulin was 3.73 per cent.

Nine and 10 are cases of xanthoma in diabetes mellitus. The globulin was increased, and the albumin was normal or slightly increased. The albumin-globulin quotient was decreased. The fibrinogen was increased. The patient in case 10 was put on insulin treatment. The albumin-globulin quotient improved, but the clinical condition remained unchanged.

Table 7 shows the analyses in four cases of acute nephritis and in eight cases of chronic glomerular nephritis.

In case 1, the blood picture during the recovery from a mild acute nephritis following measles in a man, aged 19, is shown. The first analysis gave an albumin-globulin quotient of 1.5, due to an increased globulin concentration (3.11 per cent). The fibrinogen was 308 mg. per hundred cubic centimeters. The urine showed numerous casts and

TABLE 7.—*Acute Nephritis and Chronic Glomerular Nephritis*

Case	Date	Sex	Per Cent Serum			Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma				Mg. per 100 Cc. Blood			Comment
			Albumin	Globulin	Total Protein			Fibrinogen	Cholesterol	Calcium	Inorganic Phosphorus	Non-protein Nitrogen	Uric Acid	Creatinine	
1	9/10/26	M	4.54	3.11	7.65	1.5	47.3	308	249	9.5	3.2	37	...	...	Acute nephritis, mild, following measles
	12/20/26		4.06	2.14	6.20	1.9	44.0	195	178	10.6	....	29	4.2	...	Improved, less casts and red blood cells in urine
	7/ 6/27		4.70	2.22	6.92	2.1	42.0	214	151	....	3.6	31	3.2	...	No casts, no red blood cells in urine
2	2/11/27	M	5.08	3.52	8.60	1.5	27.5	455	139	....	....	158	5.4	4.9	Acute nephritis; died ten days later
3	3/ 1/26	F	2.37	2.06	4.43	1.2	36.4	563	...	....	....	126	3.5	3.0	Acute nephritis
	3/ 8/26		1.56	2.12	3.68	0.7	36.2	406	186	....	16.1	240	5.1	4.6	
	3/15/26		1.65	4.25	5.90	0.4	30.5	511	190	....	18.3	187	4.2	3.6	Died next day
4	10/ 3/27	M	3.58	3.75	7.33	0.9	23.0	377	128	10.2	4.3	80	2.8	2.0	Acute nephritis; hematuria; died four weeks later
5	4/ 4/26	F	3.41	2.40	5.81	1.5	37.8	350	...	9.4	....	47	...	...	Chronic glomerular nephritis; blood pressure, 220/130; coryza;
6	2/ 4/27	F	3.07	2.49	5.56	1.2	34.7	532	357	....	....	47	3.6	3.0	Chronic glomerular nephritis; infected tonsils; pyorrhea
	7/27/27		2.57	2.17	4.94	1.2	26.6	422	178	....	3.5	53	6.7	...	Albuminuria and casts
7	3/ 5/25	F	3.06	2.96	6.02	1.0	....	730	160	....	....	55	3.0	...	3 g.p.l.
	4/11/26		4.60	1.95	6.55	2.4	39.5	520	...	9.8	....	28	...	...	Chronic glomerular nephritis; blood pressure, 250/130; ur. alb.
															Phenolsulphonphthalein test 1 hour 40% excretion; blood pressure, 218/120
	3/ 9/27		3.89	2.26	6.15	1.7	....	466	134	9.9	....	36	...	...	Blood pressure, 210/125
	7/10/27		3.53	2.18	5.71	1.6	31.8	612	...	10.2	4.3	40	2.5	...	
	4/29/29		3.48	2.20	5.68	1.6	37.8	582	122	....	4.4	44	2.9	...	Blood pressure, 210/120
8	1/13/26	M	3.13	1.22	4.35	2.6	39.2	294	...	9.9	....	47	3.1	2.3	Chronic glomerular nephritis; blood pressure, 165/110
	5/26/26		4.71	1.54	6.25	3.1	37.8	414	276	9.8	4.6	61	6.1	2.2	Nausea and vomiting; blood pressure, 205/125
	8/18/26		3.15	2.50	5.65	1.3	30.6	373	211	8.9	5.2	94	3.6	4.1	Phenolsulphonphthalein test 1 hour 5% excretion; blood pressure, 210/145
	8/30/26		3.15	1.70	4.85	1.9	27.5	325	200	9.3	6.5	95	4.7	7.6	Feels improved; played golf; blood pressure, 185/128
	9/17/26		2.64	2.11	4.75	1.3	27.2	348	174	9.0	10.1	138	8.1	4.2	Bed; blood pressure, 220/140; died 6 days later
9	5/17/27	F	2.90	1.25	4.15	2.3	36.8	518	415	8.8	....	50	15.0	3.6	Chronic glomerular nephritis; plasma chloride as sodium chloride, 755 mg. per hundred cubic centimeters
	5/20/27		3.14	1.01	4.15	3.1	36.8	396	358	8.0	3.5	30	3.0	1.5	Plasma chloride as sodium chloride, 707 mg. per hundred cubic centimeters
10	5/16/27	F	2.76	1.58	4.35	1.7	25.2	300	400	9.1	5.4	35	3.8	...	Chronic glomerular nephritis
	6/ 8/27		2.38	1.60	3.98	1.5	24.5	435	294	9.6	5.4	36	...	...	
11	10/20/27	F	4.55	1.10	5.65	4.0	32.6	256	300	10.4	5.9	62	6.0	3.8	Chronic glomerular nephritis
12	1/12/27	M	3.95	1.80	5.75	2.2	18.8	578	...	10.0	....	107	4.9	9.1	Chronic glomerular nephritis; died 14 days later
13	10/10/27	M	4.25	1.50	5.55	3.3	26.6	333	203	8.3	8.9	30	5.0	...	Chronic glomerular nephritis; died three months later

a one plus albumin reaction. Three months later the globulin had decreased to 2.14 per cent, the fibrinogen was 195 mg. per hundred cubic centimeters and the quotient was 1.9. Seven months after this analysis there was a further increase in the quotient, due to a rise in the albumin fraction; the fibrinogen was 214 mg. per hundred cubic centimeters. The urine showed no casts and only a faint trace of albumin.

The patient in case 2 came to the clinic with acute nephritis and died ten days later. The quotient was 1.5 with a normal albumin concentration and a globulin concentration increased to 3.52 per cent. There was considerable retention of nitrogen.

The patient in case 3, a girl aged 16, died within fifteen days. The globulin rose from a concentration of 2.06 to 4.25 per cent the day before death. Coincident with this increase there was a decrease in the albumin fraction from 2.37 to 1.65 per cent on the last analysis. The fibrinogen was markedly increased.

Patient 4 had a subacute nephritis with pronounced hematuria. He died about four weeks after the date of the reported analysis. The albumin-globulin quotient was 0.9, mainly due to the increased globulin concentration of 3.75 per cent. There was moderate azotemia.

In cases 5 and 6 the patients had chronic glomerular nephritis with mild infections. The patient in case 5 (coryza with elevation of temperature at the time of analysis) showed a quotient of 1.5, and the patient in case 6 (infected tonsils and pyorrhea) had an albumin-globulin quotient of 1.2 on two occasions. Case 7 (chronic glomerular nephritis) has been followed since 1923. The slightly increased globulin and the invariably high fibrinogen lead one to suspect a focus of infection in this case.

Case 8 was followed for three years, and the analyses during the last year of life are shown. On only one occasion was the globulin found to be increased (2.50 per cent), and six days before death its concentration was 2.11 per cent. The albumin-globulin quotient fell from 2.6 to 1.3, but the reduction in the quotient is due to the decrease in the albumin fraction. The fibrinogen was slightly increased.

Cases 9 to 12 are ambulant cases of chronic glomerular nephritis. None of these cases showed an increased globulin concentration. The patient in case 12 (globulin 1.80 per cent) came to the clinic with a severe retention of nitrogen (nonprotein nitrogen 167 mg. per hundred cubic centimeters, creatinine 9.1 mg. per hundred cubic centimeters). He died within a week.

In glomerular nephritis, uncomplicated by an infection, the serum proteins do not vary considerably from the normal. There is a tendency to a decreased albumin concentration, and this becomes more pronounced in the later stages. The fibrinogen may be normal or slightly increased.

Table 8 gives the plasma proteins in five cases of nephrosis. Case 1 has been followed since 1923. The globulin occasionally rise above the normal, but only slightly. A mild respiratory infection was present at the time. The albumin was materially decreased. The average serum protein concentrations (fifteen analyses) were: albumin, 2.08 per cent; globulin, 2.01 per cent. The fibrinogen and cholesterol were much increased in concentration. With improvement in the clinical condition the albumin increased in concentration, and the albumin-globulin quotient rose.

Case 2 presents a similar picture. The albumin was much decreased and the globulin was normal or only slightly increased. The average concentrations (seven analyses) were: albumin, 2.10 per cent; globulin, 2.30 per cent.

Case 3 also had a much reduced albumin concentration (1.57 per cent) which gradually increased to 2.47 per cent. The average concentrations of the six analyses in this case were: albumin, 2.36 per cent; globulin, 1.75 per cent.

The low albumin-globulin quotient in cases 4 and 5 is also attributable to the low albumin concentration. Case 6, an ambulent clinic case, showed the unusual phenomenon of decreased albumin concentration with a correspondingly decreased globulin concentration. The patient in this case, unfortunately, was lost sight of after two examinations, but the averages of these two closely corresponding determinations were: albumin, 2.36 per cent; globulin, 0.54 per cent; albumin-globulin quotient 4.3. The fibrinogen concentration was normal. The cholesterol was much increased.

None of these patients showed any retention of nitrogen. All had intense albuminuria, casts and renal epithelial cells in the urine, edema and low basal rate. The calcium concentrations were always below normal, the cholesterol was invariably much increased and the fibrinogen concentrations, with the exception of that in case 6, were much increased. Improvement in the clinical condition reflected itself in an increase in the albumin concentration. Coincident with this increase in the albumin concentration there may be a slight decrease in the globulin and fibrinogen concentrations.

COMMENT

Assuming the serum proteins to be formed outside the circulation, one may consider the liver, and the intestinal mucosa as well as the blood-forming organs as the most likely sites of formation. The entrance of the proteins into the blood stream will be governed by the state of endothelial permeability in these organs. It is known that the normal endothelium, with the exception of the capillaries in the liver, in the intestinal mucosa and possibly the lungs is impermeable to the plasma

TABLE 8.—*Nephrosis*

Case	Date	Sex	Per Cent Serum			Albumin-Globulin Quotient	Cell Volume, per Cent	Mg. per 100 Cc. Plasma				Per Cent Blood		Comment
			Albumin	Globulin	Total Protein			Fibrinogen	Chlorides as NaCl	Cholesterol	Calcium	Non-protein Nitrogen	Uric Acid	
1	12/ 5/23	M	1.08	2.72	3.80	0.4	38.5	661	564	443	8.4	30.0	..	Urine albumin; 6.8 g.p.l., few f. gr. and hyal. casts; R.B.C. and renal cells; P.S.P. test (12/5/23) 1 hr. intraven. 40% excretion
	1/ 4/24		1.46	1.34	2.80	1.1	33.0	1,000	594	425	8.7	35.0	2.5	
	2/ 8/24		1.93	1.73	3.66	1.1	40.0	770	...	395	8.5	....	...	
	3/ 7/24		1.78	2.30	4.08	0.8	40.5	585	640	445	8.0	....	...	Basal rate, —33%; blood pressure, 150/90
	6/ 5/24		2.34	2.16	4.50	1.1	39.0	625	607	...	8.3	40.0	4.7	
	9/25/24		1.98	1.86	3.84	1.1	43.0	650	...	226	8.2	37.0	3.4	
	1/ 8/25		2.18	2.12	4.30	1.0	40.1	650	625	278	7.6	41.0	2.0	
	4/30/25		2.22	1.54	3.76	1.4	42.3	606	640	...	7.1	31.0	3.7	
	7/27/25		1.55	2.21	3.76	0.7	39.8	605	585	357	8.4	31.0	4.8	
	9/17/25		1.90	2.95	4.85	0.7	41.7	755	610	288	7.3	32.0	4.2	
	2/ 5/26		2.16	1.68	3.84	1.3	42.8	735	585	455	7.6	40.0	...	
	7/21/26		3.13	2.75	5.88	1.1	45.0	745	...	360	9.9	35.0	2.8	Basal rate, —8%; blood prssure, 135/80; improved, feels well
	12/ 8/27		3.08	1.74	4.82	1.8	45.5	395	625	250	9.5	32.0	...	
	2/23/28		2.50	1.17	3.73	2.2	41.4	340	595	210	8.5	29.0	2.9	Greatly improved clinically
2	6/12/24	M	2.07	2.50	4.57	0.8	41.7	667	582	606	8.5	35.0	1.5	Urine albumin, 7 g.p.l., many casts, few red blood cells and renal cells
	7/ 8/24		2.08	2.83	4.91	0.7	37.6	700	...	476	8.0	40.0	3.2	Blood pressure, 98/70; basal metabolic rate, —34%; 1 hour P.S.P. test intraven. 50% excretion
	7/17/24		2.27	2.63	4.90	0.9	39.0	750	...	418	8.7	38.0	3.3	
	9/11/24		2.16	1.93	4.09	1.2	42.5	550	654	568	8.2	36.0	3.0	
	10/ 2/24		1.87	2.04	3.91	0.9	42.0	520	681	417	8.1	30.0	...	
	11/ 5/24		2.16	2.14	4.30	1.0	40.3	580	583	447	7.8	30.0	...	
	11/18/24		2.12	2.08	4.20	1.0	40.0	745	566	...	7.9	30.0	...	Decrease in casts; basal rate—8%
3	10/ 6/26	M	1.57	1.92	3.49	0.8	36.5	642	627	560	8.0	30.0	...	Urine albumin 6 g.p.l., many casts, blood pressure, 100/70; basal rate, —8%
	10/25/26		1.82	1.79	3.61	1.0	36.5	1,070	617	446	9.0	24.0	2.8	Pyorrhea of lower gums; edema
	1/18/27		2.61	1.55	4.16	1.7	32.0	580	606	460	9.3	32.0	...	
	5/10/27		2.88	1.42	4.30	2.0	38.0	566	642	352	9.2	32.0	2.2	
	6/28/27		2.09	1.91	4.60	1.4	35.0	495	620	357	9.7	39.0	2.2	
	9/12/27		2.47	1.83	4.30	1.4	39.0	650	612	288	...	32.0	...	Improved; number of casts reduced; feels well; no edema
4	9/22/27	F	0.97	1.55	2.52	0.6	26.9	580	560	760	7.2	44.0	...	
5	3/ 1/26	F	1.63	2.30	3.93	0.7	36.0	450	...	...	...	29.0	3.2	Intense albuminuria, many casts, edema, headaches
	3/15/26		2.47	1.58	4.05	1.6	37.2	480	655	333	8.6	29.0	2.5	
	5/11/26		2.33	2.35	4.68	1.0	....	483	620	333	8.5	29.0	...	
6	12/23/25	M	2.38	0.50	2.88	4.7	....	286	...	242	9.0	33.0	3.1	Albuminuria, 5 g.p.l., many granular and fatty casts
	12/31/25		2.35	0.59	2.94	4.0	48.5	...	600	202	9.1	30.0	...	
7	3/ 3/24	F	0.83	2.01	2.84	0.4	38.0	1,020	524	148	8.3	24.0	1.5	Intense albuminuria; intercurrent fatal pneumonia
			0.78	2.16	2.94	0.4	37.5	1,530	...	...	...	....	...	

proteins.[6] The capillaries of the bone-marrow, the spleen and the blood-forming organs as a whole are permeable to the formed elements of the blood and may be assumed to be permeable to the plasma proteins. The greatest known endothelial permeability is in the liver. The lymph from the liver approximates the plasma in its protein concentration. The lymph secreted by the intestinal mucosa contains only about two thirds of the plasma protein concentration, and it is assumed that only the smaller molecules pass out.[7] If the serum proteins enter and escape the circulation as entities, and are only partly or not at all broken down while in the circulation, their relative concentration will depend also to a certain degree on the state of capillary permeability in other parts of the organism. Petersen, reasoning on the basis of anatomic structure and obvious function, made the assumption that the capillary endothelium has become specialized in the control of permeability. "If the endothelial wall of the capillaries acts in the manner of an ultra filter, allowing water, crystalloids and in some cases colloids to pass through, then any change in this ultra filter will be accompanied by a change in the relative concentrations of the colloids of different viscosities which it allows to pass through."[8] Heightened permeability of the capillaries may be brought about by any of the factors which cause increased permeability of the cell, by dilatation due to physical, nervous or chemical stimuli,[9] by increased capillary pressure or by injury.[10]

The proteins of the plasma which may be isolated by chemical methods are, in the descending order of their viscosities, fibrinogen, euglobulin, pseudoglobulin and albumin. The greater viscosity of the globulin fraction is mainly due to the euglobulin which constitutes approximately 46 per cent of the fraction and has a viscosity of 1.21 for a 1 per cent aqueous solution. The viscosity of a 1 per cent pseudoglobulin solution is 1.12, and the viscosity of the globulin fraction in like concentration is 1.16. The viscosity of a 1 per cent albumin solution is 1.08. The viscosity of water is taken as 1 in these measurements.

The viscosities of the serum proteins parallel their "molecular weight" as determined by the centrifugal method. Svedberg[11] obtained

6. Krogh, A.: Anatomy and Physiology of the Capillaries, New Haven, Conn., Yale University Press, 1924, p. 230.

7. Krogh (footnote 6, p. 231).

8. Petersen, W. F.; Levinson, S. A., and Hughes, T. P.: Studies in Endothelial Permeability; Effect of Epinephrin on Endothelial Permeability, J. Immunol. **8**:323, 1923.

9. Krogh (footnote 6, p. 323).

10. Landis, E. M.: Micro-Injection Studies of Capillary Permeability, Am. J. Physiol. **81**:124, 1927.

11. Svedberg, T., and Fahrseus, R.: A New Method for the Determination of the Molecular Weight of the Proteins, J. Am. Chem. Soc. **48**:430, 1926. Svedberg, T., and Sjogren, B.: The Molecular Weights of Serum Albumin and Serum Globulin, J. A. Chem. Soc. **50**:3318, 1928.

by this method the value of 67,500 for serum albumin and 103,800 for serum globulin. Svedberg considered these fractions as entities and questioned the existence of euglobulin and pseudoglobulin preformed in the serum.[12] Sørensen, on the other hand, considered that the formula $E_n P_m$ when n and m are variables, expresses the composition of the serum globulin fraction. He considered euglobulin an addition product of pseudoglobulin and a lipid.[13] The mechanism of the rise of the globulin fraction in infections and toxemias is not explained. This may possibly be a defensive mechanism to combat the infection or result from the changed conditions due to the infection itself. Many investigators attribute the significance of the globulins in infections to the addition-combination with a lipid. Troensgaard and Koendahl [14] stated that a cholesterol-globulin complex is the important factor. One may assume that the greater viscosity of the euglobulin fraction as compared to the pseudoglobulin is due to an addition or combination of the pseudoglobulin with a lipid-like substance.

To the view that the serum proteins are formed outside the circulatory system and that the relative impermeability of the capillary endothelium as a whole prevents the escape of the serum proteins, the difference in size and viscosity between the two fractions is of importance. The partial or complete permeability of the capillaries in certain organs and the changes in capillary permeability in disease are also relevant. A shift in the relative concentrations of the fractions, due to a relative and absolute increase in the globulin fraction, may from this point of view indicate greater permeability in the organs which are the main sources of the serum proteins as well as increased production or decreased destruction of that fraction. It may also indicate a decrease in euglobulin formation with a consequently greater influx of the less viscous part, the pseudoglobulin. On the other hand, a shift in the albumin-globulin quotient due to an absolute decrease in the albumin fraction may denote increased permeability in the capillaries normally impermeable to the serum proteins, as well as lessened production or increased destruction of the smaller molecule. The greater protein concentration and the relatively greater globulin concentration of inflammatory exudates as compared to transudates, illustrate the effect of increased permeability as it is present in inflammations. Robertson considered an altered permeability of the tissue cells in infections as the possible cause

12. Editorial, J. A. M. A. **92**:233 (Jan. 19) 1929.

13. Sørensen, S. P. L.: On the Solubility of the Serum Globulins, Comptes rendus des traveaux du laboratoire de Carlsberg **15**:14, 1925.

14. Troensgaard, N., and Koendahl, B.: Cholesterian als prostetische Gruppe im Serum Globulin, Ztschr. f. physiol. Chem. **153**:111, 1926.

of the change in the albumin-globulin quotient.[15] Prolonged ether or chloroform anesthesia, with its known effect on cellular permeability has been shown to cause a decrease in the albumin-globulin quotient owing to a decrease in the albumin fraction and an increase in the globulin fraction.

The changes found in the relative concentrations of serum proteins and fibrinogen in infectious conditions point to increased permeability. The fibrinogen is increased, the albumin is decreased slightly in the milder infections which do not affect the globulin concentrations and decidedly in the more severe and fatal infections. In the more severe infections the globulin is increased. In fatal infections the globulin is materially increased, and the increase parallels the progress of the condition.

The changes found in certain liver and gallbladder conditions differ from those encountered in the more severe generalized and localized infections. In cirrhosis of the liver there is a gradual, relatively mild decrease in the albumin fraction and a moderate rise in the globulin concentration. The fibrinogen may be slightly increased at the onset, but decreases to a low normal level and below that as the condition progresses. Concurrent infections cause only a slight increase in the fibrinogen concentration, while the response in the serum proteins is exaggerated, even in mild infections. This relationship, increased globulin concentration with a normal or even subnormal fibrinogen concentration, was not found in any of the infections studied, except when there was evidence of liver insufficiency. It was present in the case of myelogenous leukemia and in the case of benzene poisoning, conditions in which the bone-marrow is known to be affected. Is the moderate rise in the globulin in these cases due to an increased release from the bone-marrow? Petersen noted that during portal blockade the fibrinogen in the lymph is reduced, while the relation between albumin and globulin remains unaltered. He stated that "assuming the fibrinogen comes from the liver this reduction can be explained by assuming that the fluid coming through comes from parts of the splanchnic area other than the liver. As soon as the blockade results in capillary injury there is increase in the fibrinogen, globulin, sugar and bile pigment."[16] Howe[1] considered it most likely that other tissues aside from the liver are concerned in the production of the serum proteins and that the mechanism of the formation of fibrinogen differs from that of the globulins. If the liver is the

15. Robertson, T. B.: Principles of Biochemistry, Philadelphia, Lea & Febiger, 1924, p. 38.

16. Petersen, W. F.; Jaffe, R. H.; Levinson, S. A., and Hughes, T. P.: Studies in Endothelial Permeability III. The Modification of the Thoracic Lymph Following Portal Blockade, J. Immunol. **8**:361, 1923.

main source of the fibrinogen while the serum proteins are derived from other sources as well, e. g., the blood-forming organs and the intestinal mucosa, it is understandable that in a condition in which the liver becomes less permeable the fibrinogen concentration in the blood becomes reduced, while the globulin concentration remains unaltered or is increased and the albumin concentration is reduced. Decreased fibrinogen concentrations have been demonstrated in extensive injury to the liver. Decreased fibrinogen concentrations in cirrhosis of the liver is mentioned by Pickering.[17] Fibrinogen is extremely variable in its concentrations; the range of the physiologic concentrations is wide. It is found slightly increased during the menstrual period, increased during the later months of pregnancy and during puerperium. It is increased in even slight infections, after exposure to x-rays, small doses of liver poisons and in all suppurative and inflammatory processes. Any irritation of the liver seems to call forth an increased fibrinogen concentration in the blood plasma. If this increase does not take place, although the clinical blood picture as a whole point to a condition which ordinarily would result in irritation of the liver and increased fibrinogen concentration, one may conclude that the liver function is impaired. Such a change in the relative concentrations is well expressed by the globulin-fibrinogen quotient.

The average physiologic globulin-fibrinogen quotient is 6.8 for males and 6.2 for females. In the cases of localized and generalized infections shown in table 4, it is generally below the average normal. It ranges between 2.2 and 11.6 and the average of all the cases is 5. It is increased and above the normal in the cases of severe and fatal infections, due to the great increase in the globulin concentrations. It was also found to be slightly increased in two cases of syphilis in which the patients had not been treated and in a case of arrested pulmonary tuberculosis in which the icteric index was 12. However, even though increased in these cases, the increase is slight when compared to the quotients found in the cases of hepatic cirrhosis. In these cases the quotient ranges between 6.5 and 24.7, and the average of the cases reported is 11.5. As the condition progresses, the quotient increases; it is an index of the severity of the condition. The increase in the globulin-fibrinogen quotient in these cases is due to the relatively low fibrinogen concentrations, while in the fatal infections it is mainly due to the material increase in the globulin concentration.

In jaundice without elevation in temperature there is likewise a temporary increase in the globulin fraction with or without a simultaneous decrease in the albumin fraction. There is practically no varia-

17. Pickering, J. W.: The Blood Plasma in Health and in Disease, London, W. Heinemann, 1928, p. 24.

tion in the fibrinogen concentration. In cholecystitis and in jaundice due to the use of arsphenamine increase in fibrinogen concentration is present, and the albumin-globulin quotient is reduced, owing to an increase in the globulin concentration and a decrease in the albumin concentration. The blood picture in the latter conditions is similar to that of other infections, but the rise in the globulin is more marked and the rise in the fibrinogen less so.

In chronic glomerular nephritis the total serum protein concentration is somewhat reduced with a normal or slightly reduced globulin. The main reduction takes place in the albumin fraction. The fibrinogen is often found to be increased. In acute nephritis there is an increase in the globulin fraction, an increase in the fibrinogen and the albumin is decreased. The changes in the proteins in acute nephritis are similar to the concentration changes found in infectious conditions.

The marked decrease in the albumin fraction is a familiar picture in nephrosis. The abnormally low albumin-globulin quotient in these cases is entirely due to this decrease. The blood picture on the whole is one of increased permeability. The calcium concentration is reduced below the normal and the cholesterol and fibrinogen concentrations are much increased, especially if edema is present.

One of the functions of the plasma proteins is the maintenance of equilibrium between the hydrostatic (filtration) pressure of the blood and the difference in osmotic pressure between the blood and tissue fluids. The capillaries are permeable to crystalloids, and normally any difference in these constituents is equilibrated. The protein content of the blood, however, is higher than that of the tissue lymph, and it is this difference in osmotic pressure which counterbalances the hydrostatic pressure which filters off the water. The effective osmotic pressure of the human serum is approximately 40 cc. of water column. It is mainly due to the albumin concentration, which contributes 7.54 cm. of column per gram of albumin in 100 cc. of serum against 1.95 cm. of column for every gram of globulin in 100 cc. of serum.[18] A low albumin concentration will therefore affect the osmotic pressure of the blood far more than a lowered globulin concentration. The edema of nephrosis is a filtration edema due to a lowered colloid osmotic pressure.[19] The red corpuscles by imbibition of water, thereby diminishing the water content of the plasma, may also take part in the regulation of the osmotic

18. Govaerts, Paul: La formation des oedemes, Bull. d. l'acad. roy. de méd. de Belg. **7**:356, 1927.

19. Iversen, P., and Nakazawa, F.: Ueber die Biochemie des Filtrationsoedem, Biochem. Ztschr. **191**:307, 1927.

pressure.[20] The corpuscular volume in filtration edema is often higher than could be expected from a determination of the red blood cell count.

The picture obtained in cases of nephrosis is in certain respects the opposite of that obtained in the diseases of the liver and gallbladder. The total serum protein concentration is much reduced, and the reduction is in the smaller molecule, i. e., the albumin fraction. The cholesterol and fibrinogen are much increased. If in the hepatic cases and in the infectious conditions one considers the rise in the globulin concentrations as due to a greater permeability in the organs which are sources of the serum proteins, one may consider the low albumin concentration in nephrosis as due, or partly due, to a heightened permeability of the capillaries normally not permeable to the serum proteins. Likewise the moderate decrease in the albumin concentrations in infections and the hepatic cirrhosis may be ascribed to increased peripheral capillary permeability. The increase in fibrinogen as well as cholesterol in nephrosis can be ascribed to a greater release of these substances on account of a general increased cellular permeability.

SUMMARY

The two fractions of the serum protein, the albumin and globulin and the plasma fibrinogen together with other blood constituents significant of the clinical condition have been determined in diabetes mellitus, benign glycosuria, localized and generalized infections, diseases of the liver and the gallbladder and in renal conditions.

The methods used and the physiologic concentrations determined by these methods are stated.

The plasma proteins are within the physiologic limits in diabetes mellitus and in benign glycosuria.

In infections the albumin is decreased, slightly in mild cases and decidedly in the more severe infections. The fibrinogen is increased, even in slight infections which do not call forth an increased globulin concentration. In the more severe infections the globulin is increased, and the increase parallels the severity of the condition.

In cirrhosis of the liver the albumin is decreased and the globulin is increased. The changes in the serum protein concentrations, however, are not so marked as in the infectious conditions. The fibrinogen is a low normal or decreased. In jaundice without elevation of temperature, the serum proteins are normal or increased, the albumin is generally within the normal limits and the globulin is increased. The fibrinogen remains within the normal limits. In cholecystitis and in jaundice due to the use of arsphenamine the picture is similar to that found in infections.

20. Schade, H.: Die physikalische Chemie in der inneren Medezine, ed. 3, Leipzig, Theodore Steinkopff, 1923, p. 178.

In chronic, glomerular nephritis, in the absence of an infection, the serum proteins are slightly reduced, especially the albumin fraction. The fibrinogen is often slightly increased. In acute nephritis the changes found are the same as in infections. In nephrosis the albumin is materially decreased, the globulin is normal and the fibrinogen is much increased.

The significance of the changes in the protein concentrations and their bearing on questions of site of formation, port of entry and functions are discussed. The importance of complete chemical analytic studies and the recognition of complications which may mask the results expected from the pathologic condition studied are evidenced. The difference in relationship of globulin to fibrinogen in infections and disturbed hepatic function is pointed out. The diagnostic and prognostic value of changes in the albumin-globulin quotient and in the globulin-fibrinogen quotient is discussed.

POSTOPERATIVE RESULTS IN TOXIC GOITER*

NORMAN E. CLARKE, M.D.
AND
IRENE BLACK
DETROIT

Since Moebius [1] in 1886 focused attention on the causative association of the thyroid with the disease which is now called hyperthyroidism, surgical intervention has become the almost universal therapeutic agent for relief from this condition. During the past fifty years the number of operative cases has increased enormously, yet there are surprisingly few accurate follow-up studies for determining what results thyroidectomy has produced on these patients. There is wide variation in the successful operative results reported in the relatively few postoperative studies. In a group of thyroidectomies reviewed one year later at the Lahey Clinic,[2] it was claimed that cure was obtained in 92 per cent. In a series of cases which includes both exophthalmic and toxic adenoma, reported by Judd,[3] it was stated that 65 per cent of the patients having severe hyperthyroidism were cured, while 80 per cent who had toxic adenoma were relieved from their toxic symptoms and cured. Among the German surgeons [4] there have been reports of cure in 30 per cent of cases of hyperthyroidism following thyroidectomy, while Bram [5] expressed the belief that a fair estimate is 18 per cent for those patients who remained cured by thyroidectomy after a lapse of several years. With the exception of the report made by Lahey, most of the other investigators have depended on mailed questionnaires for their information.

In our own report we have set up definite criteria for the judging of post-thyroidectomy results, these being (*a*) personal examination and questioning of the patient, (*b*) obtaining of the patient's basal metabolic rate, (*c*) the avoidance of pointed direct questions, eliciting informa-

* Submitted for publication, Nov. 22, 1929.

* From the Cardiac Service, Grace Hospital.

1. Moebius, P. J.: Vom Verhaltnisse der Polioencephalitis zur Basedowcshen Krankheit en Jendrassik, in Schmidt, E.: Jahrb. d. Med. **210**:237, 1886.

2. Smith, L. W.; Clute, H. M., and Strieder, J. W.: Surg. Gynec. Obst. **46**:325 (March) 1928.

3. Judd, E. S.: Results of Operation for Adenoma with Hyperthyroidism and Exophthalmic Goiter, Ann. Surg. **72**:145, 1920.

4. Quoted by Bram (footnote 5).

5. Bram, Israel: Goiter; Nonsurgical Types and Treatment, New York, The Macmillan Company, 1924.

tion without the use of suggestion and (*d*) the collection and correlation of the data by one other than the surgeon. The present lack of careful follow-up studies of the end-results of thyroidectomy by personal questioning and examination of patients a few years after operation is worthy of consideration in view of the sureness with which the surgeons have attacked this problem.

Common experience shows the striking immediate effect of surgical intervention for hyperthyroidism in most instances, but the condition of patients months or years after operation has been performed alone furnishes the true facts on which we may evaluate the real benefits of thyroidectomy. Many features other than the surgical removal of thyroid tissue may be factors in the immediate improvement. The hospital and the surgical experience have a powerful psychotherapeutic value; the rest before and after the operation have proved to be of great benefit, while the reaction with elevation in temperature, resorption of hemolyzed blood and the traumatic changes to the gland may be of unknown value.

The present study of the end-results of thyroidectomy consists of two parts. In the first part we have summarized the pertinent observations on the condition of 181 patients admitted to Grace Hospital during 1927 with a diagnosis of toxic goiter, who were later operated on. In the second part we have summarized similar pertinent observations on many of the same patients after an average time of two and one-half years had elapsed following the operation. We felt that any beneficial results obtained through thyroidectomy would have been consummated within two and one-half years and likewise that most untoward results would be present within the same time. In order to secure as great accuracy as possible, letters were written to this group of patients asking them to return. All those who did were examined and their interval history obtained, obviating the dangers and inaccuracies of mailed questionnaires. A basal metabolism test was also performed on practically all patients who presented themselves for this study.

INCIDENCE AND SYMPTOMS

Distribution According to Sex and Age.—Of the 181 patients whose records were reviewed, 34 were males and 147 females. The age grouping of the males showed 8 in the third decade, 11 in the fourth decade, 7 in the fifth decade and 8 in the sixth decade of life. The females showed 8 in the second decade, 46 in the third decade, 44 in the fourth decade, 25 in the fifth decade, 22 in the sixth decade and 2 in the seventh decade of life. The disproportion between the males and females, a little better than 4.3 females to 1 male, conforms to the usual experience, others reporting even higher ratios. The difference in age grouping is important, for while the males show a fairly equal distribu-

tion in the decades from 20 to 60 years of age, the greatest incidence among the females is between the ages of 20 and 50 years, or the period of active sexual life or child-bearing. This relationship of sex with the disease is somewhat substantiated, as we show in a later table, by the observed frequency of symptoms of toxic goiter occurring coincident with pregnancy.

Duration of Symptoms.—The duration of the symptoms, or the period which elapsed between the time when the disease was first observed until operation, was not stated in 23 records. Of the 158 patients who were able to give a definite time for the onset of the symp-

Chart 1.—Chart showing distribution according to sex in toxic goiter, the ratio being 4.3 females to 1 male. The numbers at the bottom of each chart indicate the number of patients.

toms, 2 had noticed the symptoms for less than one month. Among the others, there were 15 whose symptoms had been present from one to three months, 27 from three to six months, 11 from six to nine months and 37 from nine to twelve months. In 22 patients the symptoms were present from one to two years, in 18 from two to four years, in 10 from four to six years, in 8 from six to ten years and in 8 over ten years. Over one half of the total number of patients had had symptoms one year or less, but a surprisingly large number, or practically one-half, had had symptoms at least one year and a little more than 16 per cent claimed to have had symptoms for four years or longer.

Incidence of Various Symptoms.—In listing the symptoms complained of by the 181 patients, we observed great variation, but also a few symptoms which were common to almost all. The most frequent symptom complained of was nervousness. This was described by many as a feeling of inward tension or trembling, not one of actual shaking or movement. The next symptom most commonly complained of was palpitation, described by some as heart consciousness associated with a very rapid heart rate, while others described it as periods of marked heart consciousness induced by exertion or emotional excitement. The third most commonly complained of symptom was dyspnea, either as shortness of the breath on lying down, as shortening of the breath on exertion or excitement or like a feeling of choking such as that induced

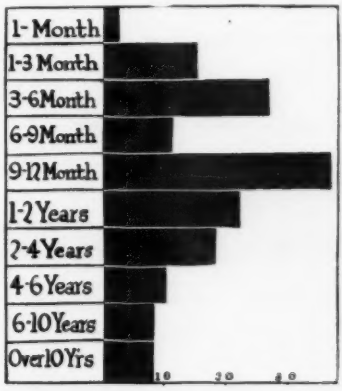

Chart 2.—A graphic presentation of the duration of symptoms in toxic goiter, time being reckoned from when symptoms were first noticed until operation.

by tracheal constriction. About one third of the patients had noticed an enlargement of their neck and a little more than one-third complained of weakness. A rather frequent complaint was irritability, while only 15 per cent had observed increased prominence of their eyes or exophthalmos. In 21 of the 181 patients, we were able to elicit a definite mental or emotional shock preceding the onset of the symptoms of toxic goiter. There were gastro-intestinal symptoms in 60 patients, most patients having two or more complaints such as diarrhea, flatulence, nausea or vomiting. The following list shows the incidence of the various symptoms in order of frequency: nervousness 156, palpitation 138, dyspnea 94, weakness 65, enlarged neck 58, perspiring 49, nausea 40, irritability 37, choking 32, vomiting 27, diarrhea 24, dizziness 23, edema of legs 23, pressure, cough, etc. 22, mental strain, emotional 21, hot

flashes 16, heart pain 15, exophthalmos 15, abdominal pain 11, abdominal distress 10, flatulence 9 and constipation 4.

The Use of Iodine.—Thirteen of the 181 patients gave a history of having used iodine salt for some time previous to the onset of their symptoms. A compound solution of iodine was given to 101 of these patients previous to their operation, while in 42, iodine was continued after operation. Apparently no distinction was made between those cases diagnosed as toxic adenoma or exophthalmic goiter in the administration of iodine, and no untoward results were mentioned with any patient, the patients with toxic adenoma apparently benefiting equally with those whose condition was diagnosed as exophthalmic goiter.

Changes in the Weight of Patients with Hyperthyroidism.—In 58 of the 181 patients no mention was made of weight or its change or lack of change with the onset of the disease. Of the 123 patients concerning whom information was available, a loss of weight had occurred in

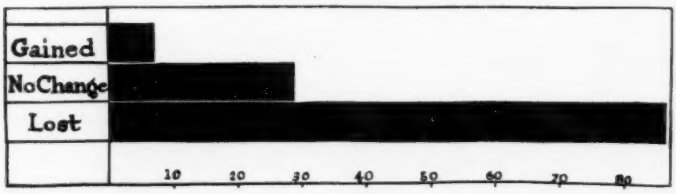

Chart 3.—The weights in 123 patients with toxic goiter showing 70 per cent losing weight while 30 per cent gained or showed no change.

87, or 70 per cent. There had been a gain of weight in 7 or 6 per cent, while the weight did not change in 29, or 24 per cent. There were, therefore, 36 patients, or 30 per cent of the entire group, in whom the disease caused no change or even allowed a gain in weight, but the great majority, 87 or 70 per cent, lost weight with the onset of hyperthyroidism.

Basal Metabolism Records.—A basal metabolism was performed on only 62 of the 181 patients previous to operation. Of these, 8, or almost 13 per cent, showed a basal metabolic reading between —10 and + 10, 11 each showed readings between + 11 to + 20 and + 21 to + 30. There were 10 patients who had basal metabolic readings between +30 and +40, while 9 were between +40 and +50 and 4 each were between +50 to +60 and +70 to +80. There were 2 between +80 and +90, while 3 showed basal metabolic rates above +90. In those cases in which more than one basal metabolic rate was taken, marked variations were observed. In 1, an initial reading was + 60 while a

second reading was +18. Another showed an initial rate of +62 with a second reading of +15. Another showed an initial rate of +42 and a later reading of —6, while others showed less but still marked variations. The ordinary basal metabolic test done in general hospitals and practice may lead to very erroneous conclusions unless rechecked and the result carefully compared with the pulse rate and general clinical observations.

Blood Pressure Records.—There were 60 patients' records which showed no blood pressure readings. Of the 121 cases in which blood pressure records were available, we have obtained the average systolic, diastolic and pulse pressure with a further classification of each division into the average mean and extreme readings. The average systolic reading for the entire 121 patients was 133 mm. of mercury. Of this number, 78 showed mean readings with an average of 119 mm. of mercury, while 43 showed extreme readings with an average of 158 mm. of mercury.

The average diastolic reading of the total number of 121 patients was 75 mm. of mercury, while 47 showed mean records which averaged 64 mm. and 74 showed extreme readings with an average of 82 mm. of mercury.

The average pulse pressure of the entire group of 121 patients was 58 mm. of mercury. Of the group, 67 patients showed mean readings with an average of 40 mm. of mercury while 54 patients showed extreme readings with an average of 68 mm.

If it is possible to interpret anything from these blood pressure readings, one could believe that there is a group represented by the 43 patients showing extreme systolic readings averaging 158 and mean diastolic readings of 64 in 47 patients in whom the disease produces an elevation of the systolic and depression of the diastolic pressure with an increase in the pulse pressure as in the 50 patients with an average pulse pressure of 93 mm. of mercury. This is frequently pointed out as characteristic of hyperthyroidism. However, this group comprises only about 37 per cent of the total number of cases of hyperthyroidism in this series while 63 per cent of those showing mean systolic readings of 119 and extreme diastolic readings averaging 82 with an average pulse pressure of 40 mm. of mercury demonstrate that at least the majority of the patients with a diagnosis of hyperthyroidism show essentially normal blood pressures.

It is more possible that this smaller group showing the higher systolic and lower diastolic readings is accounted for by the fact that approximately the same percentage of patients are found in the age group of 40 years or more, which is the time of life when essential or vascular hypertension is most prevalent.

Pulse Rates in Patients with Hyperthyroidism.—In determining the pulse rates of 178 patients, there being no records in 3 instances, we have determined (1) the average pulse rate at admission, (2) the lowest pulse rate during rest just before operation, (3) the maximum pulse rate after operation and (4) the pulse rate at the time of discharge of the patient. The average pulse rate at the time of admission for the entire group was 90 beats per minute, while in 88 showing mean pulse rates the average was 75 and for 90 patients who showed extreme pulse rates the average was 106. It is of interest that the group is practically divided into two equal parts according to the average mean or extreme pulse rates, with the difference of an average of 31 beats per minute, or in about one half of the patients the pulse rate at admission was normal while in the other half it was definitely elevated.

The average lowest pulse rate during rest before operation in the entire group of patients was 80, showing an average decline of 10 beats per minute through rest. The average low pulse rate during rest before operation of 39 patients who showed mean readings was 73 beats per minute, while in 139 patients who showed extreme rates the average was 82 beats per minute. It appears from these figures that there was a group of patients represented by the 39 or 22 per cent, showing an average mean pulse rate of 73 in whom the decline after rest was very slight, while in a larger percentage there was a definite decrease in the pulse rate after rest in bed.

The average maximum pulse rate after operation in the total number of patients was 103 beats per minute, while the average for a group of 47 patients, or 26 per cent, who showed mean readings was 92, and for 131 patients showing extreme readings it was 106. The similarity between these two groups and the groups showing low pulse rates during rest is so striking that it adds further evidence to the supposition that this series includes a rather large number of patients in whom the cardiovascular system was quite stable, even approaching the normal condition, and was influenced slightly if at all by the toxic condition as compared to the others.

The average pulse rate at the time of discharge of the entire 178 patients was 73, while in 45 who showed mean readings it was 68, and in 133 who showed extreme readings, 75.

The closely comparable divisional percentages obtained for the various pulse reactions of these patients in these last 3 groups is striking and suggests the possibility that the same etiologic factor might not have been operating in all these patients whose condition was diagnosed as toxic goiter.

The Incidence of Focal Infection.—The relationship of focal infection to hyperthyroidism has been so frequently observed and discussed

that it has even been considered as a causative agent, though it is not universally accepted as such. Unfortunately, we believe that this condition was not carefully searched for among this entire group. However, in the records we found sources of possible focal infection mentioned rather frequently but never mentioned as a possible etiologic factor. There was definite note made of infected teeth in 34 patients and of tonsillar infection in 27. The gallbladder was diagnosed as being diseased in 7 patients, while sinusitis was present in 3 and acute or subacute pelvic inflammatory conditions were considered present in 6 other patients of this group.

THE POSSIBLE PRECIPITATING CAUSES

Few patients ascribed the onset of their acute symptoms to a definite cause. There were eleven patients who associated the onset of their disease with immediately preceding acute infections while in three the onset of toxicity had been immediately preceded by an operation, one having been a tonsillectomy, another a hemorrhoidectomy and the third a pelvic operation. The most interesting preciptating cause and the most frequent was that of pregnancy, which was given as a cause by 12 women. There were 12 patients, or about 7 per cent of the total, who gave a history of having had previous thyroidectomies, some having had periods of fairly good recovery intervening while others had shown no improvement between operations, having undergone within a short time their second operative measure. Nine patients gave definite histories of acute trouble, the illness being diagnosed as nervous breakdown in the years preceding their operation. In 21 patients there had been a definite emotional shock antedating the onset of their symptoms.

THE OPERATIVE PROCEDURE AND MORTALITY

The most frequent operative procedure used on these 181 patients was a bilateral resection of both lobes of the gland, the actual amount or percentage of tissue removed not being stated in any record. A bilateral thyroidectomy was performed on 151 of the 181 patients. Adenomectomy was performed 4 times, while a subtotal resection of one lobe was performed 6 times and a total resection of one lobe 5 times. The ligation of one or more vessels as a preliminary operation was done in 2 patients, and the operative procedure was not stated in 9 instances.

Pathologic Report of the Tissue Removed.—A pathologic examination of the tissues removed by thyroidectomy was made in 151 instances; in 30 there was no examination reported. The diagnosis was colloid adenoma in 59 instances, while colloid adenoma with hemorrhage was reported twice, and with marked fibrosis in 17 specimens. Fetal

adenoma was reported 5 times, while adenomas, rapidly growing or cellular, were also reported 5 times. There was colloid adenoma with lymphoid hyperplasia and colloid adenoma with glandular hyperplasia reported respectively in 22 instances while colloid adenoma with lymphoid and glandular hyperplasia was reported 16 times. There was 1 instance each of chronic productive thyroiditis, adenocarcinoma and cystic colloid adenoma.

Mortality Rate.—Among the 181 patients operated on by the general surgical staff, 1 died while the patient was still on the operating table. This fatality was due to tracheal collapse, death being very sudden.

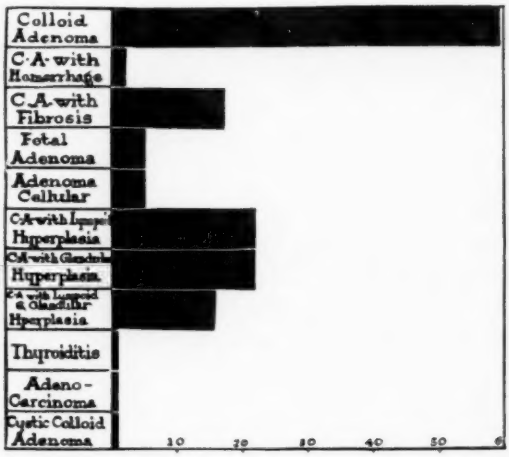

Chart 4.—Pathologic reports of thyroid tissue removed at operation, showing a predominence of the colloid adenomas with very few primary hyperplastic glands.

Nine other patients died within from twenty-four to thirty-six hours following removal of the thyroid gland, the operation being the direct cause of death in all. This makes a total mortality of 6 per cent following operation in the 181 cases of thyroidectomy. The mortality rate among those operated on by the more skilful and experienced surgeons was 2 per cent, but the general rate is raised by the death of patients operated on by the less skilled and experienced members of the department.

OPERATIVE RESULTS

Study of Seventy-Six Patients Two and One-Half Years After Thyroidectomy.—In the foregoing pages we have summarized the pertinent observations in 181 patients whose conditions were diagnosed

as toxic goiter before thyroidectomy. The present paper deals with the follow-up studies among the same group of patients after an average time of two and one-half years had elapsed after the operation. We encountered many difficulties in attempting to get in touch with these persons. The addresses of many were lost, but through letters and visits to homes and through diverse inquiries we were able to have 76 patients return for examination and basal metabolism tests. As we were strangers to most of these people, we had the advantage of being able to obtain their frank statements as to their operative results. From various experiences we believe that these people, at least in many instances, will not reveal their true condition entirely to the surgeon who operated on them. Likewise, we were able to approach their problems without bias and tried to offer no leading thoughts or suggestive questions in soliciting our information.

TABLE 1.—*Comparison of Preoperative Symptoms in Patients with Toxic Goiter with Those Present in a Group Two and a Half Years After Operation*

Symptoms of Toxic Goiter in 181 Patients Before Operation			Average 2½ Years After Thyroidectomy in 76 Patients		
Symptoms	No.	Per Cent	Symptoms	No.	Per Cent
Nervousness	156	86.0	Nervousness	32	42.0
Palpitation	138	76.0	Palpitation	28	37.0
Dyspnea	94	52.0	Dyspnea	7	9.0
Weakness	65	36.0	Weakness	48	63.0
Enlarged neck	58	32.0			
Perspiration	49	27.0	Perspiration	9	12.0
Nausea	40	22.0	Nausea	14	18.0
Irritability	37	20.0			
Choking	32	18.0	Choking	7	9.0
Vomiting	27	15.0	Vomiting	6	8.0
Diarrhea	24	13.0	Diarrhea	5	6.6
Dizziness	23	12.7			
Mental changes	21	11.5			
Edema	20	11.0	Edema	23	30.0
Exophthalmos	15	8.3			

We attempted to determine to what extent the symptoms that they had had before operation had persisted. This information was obtained by asking them to describe in what ways they felt different than before operation. No request was made for information as to specific symptoms. The following information regarding the symptoms was obtained.

The most frequent symptoms complained of, unlike those experienced before operation, was weakness, the second was nervousness and the third most commonly complained of symptom was palpitation. This varies from the incidence of symptomatic complaints before operation. Below are listed the various symptoms in order of frequency: weakness 48, nervousness 32, stronger 28, palpitation 28, edema 23, gas and bloating 19, nausea 14, sensitive to cold 10, perspiration 9, dyspnea 7, choking 7, rheumatism 7, vomiting 6, hoarseness 6 and diarrhea 5.

It is of interest that the same symptoms which were present before operation persist in such a high percentage of these people. A very interesting fact is the failure of over 50 per cent to regain normal strength and the rather frequent complaint of postoperative rheumatism with the number who complained of unusual sensitiveness to cold, edema and hoarseness. These symptoms indicate the presence of myxedema.

We believe that comparison of this table of symptoms with those before operation reveals the fact that the situation is not in line with what we desire from surgical intervention in toxic goiter.

Weight After Thyroidectomy.—In investigating the change or lack of change in the weight after operation we again found unexpected results. In these 76 patients who were operated on, 44, or 58 per cent, had gained and maintained their gain in weight two and one-half years after thyroidectomy. There were 7 who had lost weight and 25 whose present weight is practically the same as at the time of operation. This

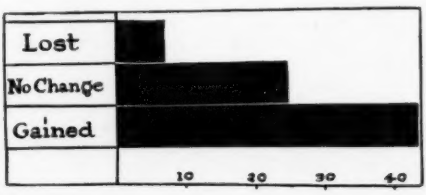

Chart 5.—The analysis of weights in seventy-six patients two and a half years after thyroidectomy showing a gain of weight in 58 per cent and loss or no change in 42 per cent.

makes a total of 32, or 42 per cent, for those who had lost, or who had shown no change in weight after thyroidectomy.

Pulse Rate After Thyroidectomy.—In determining the average pulse or heart rate, we have taken for comparison the average pulse rate for the same people at the time of their discharge from the hospital following thyroidectomy. We found that the average pulse rate in this group when they left the hospital was 80 beats per minute. The average pulse rate for this entire group now is 75, a slight decline in the total average. In obtaining the pulse rate of the means, we find this includes a group of 41 patients or 54 per cent with an average heart rate of 67, while the extremes consisted of a group of 35 patients or 46 per cent who showed an average heart rate of 86. The 41 or 54 per cent with low pulse rates of 67 closely parallels the number of patients, 58 per cent, who had gained weight, and likewise the 35 patients or 46 per cent with the average pulse rate of 86 is comparable to the 42 per cent who had lost, or had shown no change in their weight after thyroidectomy.

Basal Metabolic Test Records.—The basal metabolism reports of this group of patients, the test having been obtained on only 64 of the 76, was as follows: There were 7 who had basal metabolisms between — 10 and — 30; 43 showed a normal reading ranging between — 10 and + 10, 10 showed readings between + 10 and + 20, while 2 each showed readings between + 21 and + 30 and between + 31 and + 40.

Blood Pressure Observations.—In obtaining the average blood pressures of this group of patients, we also took for comparison the average blood pressure readings in this same group at the time of discharge from the hospital following thyroidectomy. We found that the average sys-

TABLE 2.—*A Comparison of the Mean and Extreme Pulse Rates After Operation Showing Close Correlation to the Percentage for Weights in the Group of Seventy-Six Patients*

At Time of Operation	No.	Rate	2½ Years After Operation	No.	Rate
General average of admission..	178	190	Average of group	76	76
Average of means	88	75	Average of means	41	67
Average of extremes	90	106	Average of extremes	35	86
Average low-resting rate.....	178	80			
Average of means	39	73			
Average of extremes	139	82			
Av. maximum after operation.	178	103			
Average of means	47	92			
Average of extremes	131	106			
Average of discharge	178	73			
Average of means	45	63			
Average of extremes	133	75			

tolic pressure for the group at the time of discharge from the hospital was 128 mm. of mercury, while the average for the same group now was 130 mm. of mercury, or practically identical results. The average diastolic blood pressure when leaving the hospital was 79 mm. of mercury and the average diastolic at present is 88 mm. of mercury. It is of interest that in the same group of patients there were 7 who showed a systolic blood pressure of 150 mm. of mercury or above at the time of discharge from the hospital while now there are 15. At the time of discharge from the hospital there were only 2 of the same patients with a diastolic reading of 100 mm. of mercury or over, while now there are 10 patients with abnormally high diastolic pressure, a relatively large increase in numbers over such a short period of time.

General Results of Thyroidectomy.—The most critical test of operative results depends on determining the general physical status of the patients a few years after. For this purpose we have grouped these patients under (1) those who are entirely well, (2) those showing

moderate improvement, (3) those showing slight improvement and (4) those in whom a definite thyroid toxicity has recurred and is present.

Our definition of those who are well is that the patient spontaneously expresses the same or as having been definitely cured by the operation; having none of the previous symptoms, or at least not more than one would expect in a normal person, and one in which they have gained strength and are not under the care of a physician at the present time.

We have classified as showing moderate improvement, those who express themselves in such statements as, "feeling better but the trouble is returning," or they feel that the operation has helped them, but they still have some of the symptoms and their strength is not good; also cases in which symptoms were evidently mild before operation and in which there had been no loss of weight; cases in which the few symp-

Chart 6.—The condition of seventy-six patients two and a half years postoperatively, according to our standards, shows 16 per cent cured, 40 per cent showing moderate improvement, 34 per cent showing slight improvement and a definite recurrence of toxicity in 10 per cent.

toms return periodically; cases in which the previous symptoms are better even though other symptoms have developed since, and the cases in which the patient feels, according to his statement, somewhat emotional and irritable, and those also in which the patient feels better but takes thyroid extract to maintain health.

In the group with slight improvement we have placed those patients who at the time of operation obviously had chronic nephritis or mitral stenosis, and whose symptoms still persist but are less severe; those whose general health is not good; those who evidently have a marked psychic background for the trouble, the symptoms of which still persist; those in whom there is yet a marked emotional instability; those who have a history of a nervous collapse since operation, and who are at present under the care of a physician for nervousness, heart trouble or psychiatric problems, and those who have been unable to work since the operation and have not gained weight or have lost it.

In the group of recurrence there is not only the typical picture of the toxic goiter syndrome, but also an elevated basal metabolic rate.

In the group classified as well, we found 12 patients, or about 16 per cent; of those showing moderate improvement there were 31 patients, or approximately 40 per cent; of those showing slight improvement there were 26, or 34 per cent; while there was a definite recurrence in 6, or 10 per cent. We can say, therefore, that there were 56 per cent of this group of patients who obtained sufficient relief from their thyroidectomy to enable one to classify them as average normal healthy persons, while there were 44 per cent in whom there was either a definite persistence or a recurrence of the condition, the persons not having obtained sufficient relief so that they might be considered well. In fact, many had noticed no improvement or are at present under the care of physicians for their original complaint. Again we find that these figures conform very closely to those previously mentioned in that we found 58 per cent had gained weight, whereas we noted that 56 per cent, approximately the same figure, had obtained definite worth while improvement, whereas 42 per cent had lost or shown no change in weight while 44 per cent showed slight improvement or a recurrence of their original symptoms.

Relationship of Glandular Pathology and Operative Results.—We attempted to determine whether there was any relationship between the improvement or lack of improvement and the nature of the glandular disease. The pathologic diagnosis showing the greatest incidence was colloid adenoma, there being but few with primary hyperplasia and an intermediate number showing colloid adenoma with some hyperplasia. We were unable to ascertain any relationship between improvement or lack of improvement in any of the patient's physical manifestations or present condition, with the type of pathologic process in the removed gland.

CONCLUSIONS

The immediate value of surgical intervention in acute hyperthyroidism cannot be denied, but its later benefit in all types of hyperthyroidism and the rationalism of its universal use are open to serious doubt. The methods that have been employed chiefly by surgeons in reporting their operative cures are also open to criticism. In our present confused state of knowledge concerning toxic goiter, it is essential that what information we have, whether etiologic or therapeutic, be well controlled and all sources of error, particularly such as personal factors and methods of procedure, be properly controlled and as accurate as possible. By using personal examinations instead of questionnaires, we have arrived at great accuracy and have been able to observe the many sources of error in other methods.

This study has clearly shown that all patients whose condition was diagnosed as hyperthyroidism do not conform to the same picture or manifest the same objective signs. A very important preoperative factor apparently is the patient's weight, a loss of weight being very important diagnostically and an easily obtained control for judging the probable benefit of surgical intervention. We found that 30 per cent, or almost one third, of all our patients had gained or shown no change in weight before operation, a very easily ascertainable and very important condition. In this series the same ratio, or 70 per cent losing weight and 30 per cent gaining or showing no change, was found in almost all the other clinical phases investigated. The definitely different classifications according to blood pressures, pulse rates and cardiovascular reaction to operation divided the series into two groups, the ratios very closely equaling those found for weights. Most important of all, these easily ascertainable preoperative observations are reflected in the postoperative results two and a half years later. Here we found that 42 per cent of the patients had failed to gain weight and 46 per cent showed a heart rate above normal. Also there were 44 per cent who showed but slight improvement or definite recurrence after thyroidectomy. In the postoperative group, consisting of less than one half of the entire preoperative number investigated, one cannot expect accurate approximation, but the different ratios and likewise the tendency to conformity are so striking that certain conclusions appear permissible. It is probable that the original diagnosis was erroneous in the group represented by the 30 per cent of patients who showed no loss of weight and consisted of those who manifested the toxic goiter cardiovascular syndrome but in whom the disturbance was due to a cardiac neurosis, psychiatric disturbance or other cause.

From the surgical point of view the amount of gland removed might not have been sufficient to produce the complete surgical result. It appears that weight might be a very important factor in the forming of a preoperative opinion.

It is of note that weakness persisted or was present in 63 per cent of the patients two and a half years after operation. Likewise edema, sensitiveness to cold, rheumatism and hoarseness were frequently complained of. It has been observed by Miller [6] that operative cures of hyperthyroidism are accompanied by a high incidence of myxedema. The surgeons claim that the recurrence of toxic symptoms is due to the failure to remove sufficient of the thyroid gland. They are unable to state just how much to remove, this being left entirely to experience. It might be more accurate to state that good surgical results are obtained

6. Miller, J.: Am. J. M. Sc. **177**:98, 1929.

when the surgeon removes just enough of the thyroid tissue to leave the patient in a state of balance between hyperthyroidism and hypothyroidism. Might that not be the answer to the favorable results of thyroidectomy and that chance plays a part as to whether the patient will obtain the perfect balance that leads to health or be one of the 16 per cent in our series whom we found were well? Or might chance lead to the removal of too much of the gland and produce predominating myxedema of varying degrees, the severity varying and the requirements of thyroid extract differing with its severity? These people would be like our group of 40 per cent of patients or those showing moderate relief. Again, if too much gland is left, the disease persists as in our group of 10 per cent, while if an intermediate amount is removed, the toxic symptoms persist, hyperthyroidism being predominant, somewhat alleviated by a mild myxedema as in our group of 34 per cent. It appears probable to us that the surgical removal of thyroid tissue does not in any way strike directly at the cause of the disease hyperthyroidism as evidenced by the high percentage of persistent symptoms and the fact that relief is obtained only by the development of myxedema as revealed in the incidence of postoperative complaints and the necessity for a great many patients to continue to take thyroid extract. We believe that surgical intervention is substitutive therapy only and not curative. It substitutes the dominant disease myxedema for the less dominant disease hyperthyroidism, the degree of its results in accomplishing a clinical or symptomatic cure depending entirely on chance controlled somewhat by experience. Surgical removal in no way removes the cause.

In our present state of knowledge of hyperthyroidism, surgical intervention is of undeniable value but is used too indiscriminately. A patient should be carefully studied and an opinion concerning operation given only after a careful consideration of its possible benefits to the patient. We believe that operation should be looked on only as a temporary therapeutic agent which, though not satisfactory to a large percentage of patients, is our best present agency for acute cases. Results can be greatly enhanced by careful preoperative selection.

The failure of surgical measures to produce relief for more of these patients and the fact that its application is so lacking in careful control (its results depending only on the chance ability to substitute a proper or balanced myxedematous state) shows the necessity for further study, and that the problem is primarily one for the internist.

The disease hyperthyroidism is constitutional, and even in those considered cured by operation careful examination of the patient reveals stigmas of the disease persisting. Removal of the gland interrupts only one link in the general disease, the degree of its results resting on chance.

SUMMARY

1. One hundred and eighty-one cases of thyroidectomy have been studied according to the age of the patient, distribution and duration and incidence of symptoms. It was determined that 70 per cent of the patients lost weight while 30 per cent showed no change or even gained weight. The most common pathologic process in the thyroid was colloid adenoma, hyperplasia being much less frequent. The mortality rate was 6 per cent. The pulse rate at admission, minimum before and maximum after operation with the rate at discharge were ascertained. These showed a definite division into groups according to the mean and extreme rates, the ratios conforming closely to those observed for the weight changes.

2. Seventy-six cases were studied after an average elapsed time from operation of two and one-half years. Definite rules were adhered to, namely: (1) personal examination, (2) obtaining of basal metabolic rate, (3) avoidance of direct questions and (4) collection of data by some one else than the surgeon. A high persistence of the previous symptoms was found with also those symptoms suggesting prevalent myxedema. It was found that only 58 per cent of the patients had gained weight, that the pulse rate was below normal in a group approximating the same number who had gained weight and above normal in approximately the same number who had not gained weight since operation. The blood pressure showed an unusually high number who had developed abnormally high blood pressures since operation. We classified our patients as (1) well, (2) moderately improved, (3) slightly improved and (4) those with recurrence, according to definite rules. We found 16 per cent well, 40 per cent moderately improved, 34 per cent slightly improved and 10 per cent showed definite recurrences.

3. We consider surgical intervention unsatisfactory in a large group of these patients, but we consider that its benefits could be improved by more accurate preoperative selection, the weight being an accurate preoperative guide.

4. We consider surgical intervention only substitutional therapy, substituting the dominant myxedema for the less dominant state of hyperthyroidism and not in any way altering the real constitutional condition but only alleviating it. A perfect surgical result depends on the chance development of equilibrium between the hyperthyroidism and the developed myxedema.

5. The disease hyperthyroidism is primarily a problem of the internist, and its ultimate real cure will come through real control of the constitutional condition and not by surgically interrupting one link or substituting another less disturbing symptomatic or neutralizing disease.

POSTMORTEM BLOOD CHEMISTRY IN RENAL DISEASE*

S. H. POLAYES, M.D.

E. HERSHEY, M.D.

AND

M. LEDERER, M.D.

BROOKLYN

Many controversies over diagnosis arise at postmortem examinations in cases in which renal disease plays the leading or subsidiary rôle in the cause of death. Such disputes arise because of insufficient clinical data, a situation that frequently cannot be avoided because of varied adverse circumstances. However, in the absence of all other data, information concerning only the chemical changes in the blood is frequently of great aid in postmortem diagnosis. Unfortunately, in a good number of cases even this information is not available, and since the pathologist occasionally hesitates to make a diagnosis based entirely on the structural changes of the kidney, the final diagnosis often remains permanently in abeyance.

Experiences with several such cases have suggested to us the advisability of making a postmortem examination of the blood in the hope of securing aid in diagnosis in those instances in which the blood was not examined during life. A review of the literature on postmortem chemical examinations of the blood reveals a surprisingly scant amount of information. Authorities on legal medicine,[1] who undoubtedly often meet with these problems, fail to give enlightenment on this question. The only contribution in the literature dealing specifically with this subject is that of Paul,[2] who emphasized the value of postmortem determinations of blood urea nitrogen in estimating the terminal blood urea content ante mortem. This writer, however, presents too few figures for comparison between antemortem and postmortem observations to be at all convincing. On the other hand, he does make the important observation that during the first twenty-four hours after death, the urea nitrogen and creatinine content remain fairly constant. In connection with this observation, it is interesting to note that Sander,[3]

* Submitted for publication, Dec. 7, 1929.

* From the Department of Pathology of the Jewish Hospital of Brooklyn.

1. Personal communications from medical examiners office, New York.

2. Paul, J. R.: Postmortem Blood Chemical Determinations, Bull. Ayer Clin. Lab. **9**:51, 1925.

3. Sander, F. V.: The Preservation of Blood for Chemical Analysis, J. Biol. Chem. **58**:1, 1923-1924.

in a study on the preservation of blood for chemical analysis, found that the creatinine values of unpreserved blood remained constant for six days. A similar observation had been made previously by Falk and his co-workers.[4]

In the study of the cases presented in this paper, it has been our aim to compare the nonprotein nitrogen content of the blood (urea and creatinine) obtained before and after death in order to determine whether either one alone or both of the latter can be used as an aid in determining the renal status of the case. Specimens of blood were secured from the jugular vein or right atrium as early as possible within the first twenty-four hours after death, the body having been kept in the refrigerator from the time of its delivery to the morgue. Analyses were made in 100 cases representing various types of diseases, special efforts having been made to secure specimens from persons who died of a condition clinically diagnosed nephritis. Only those cases in which blood chemical tests were performed during life were selected, so that comparisons could be made between the postmortem and antemortem observations.

The hundred cases studied have been classified into five main groups; namely, miscellaneous diseases, acute infections, intestinal obstruction, renal disease with postmortem creatinine figures of less than 4 mg. per hundred cubic centimeters of blood and renal diseases with postmortem creatinine figures of 4 mg. or more. Acute infections and intestinal obstruction have been grouped separately, because it has been frequently stated that there is a retention of nonprotein nitrogen in these cases just before death.

The time that elapsed between the death of the patient and the securing of blood for analysis ranged between one-half to twenty-four hours, the average being six and one-half hours. With few exceptions, the analyses were made immediately after the blood was secured. In no case was the examination delayed for more than ten hours, the specimen having been kept in the refrigerator during the delay.

The intervals between the examination of blood obtained post mortem and that obtained during life ranged from one hour to sixteen weeks, the average being about thirteen days. In very few cases, however, was the interval less than one day or more than two weeks.

Whenever other tests of renal function were performed, the results were recorded. The tests consisted of estimations of the phenolsulphonphthalein excretion, urea concentration tests and the diazo reaction[5] in the blood.

---

4. Falk, K. G.; Baumann, E. J., and McGuire, G.: The Chemical Investigation of Spoiled Meat, J. Biol. Chem. **37**:525, 1919.

5. Andrews, E. H.: An Unexplained Diazo-Color Reaction in Uremic Sera, Lancet **1**:590, 1924.

TABLE 1.—*Analysis of Data on One Hundred Cases*

Group	Type of Disease	No. of Cases	Number of Hours Postmortem Specimen Was Secured		Interval Between Postmortem and Antemortem Determination		Renal Function Tests		Antemortem Determinations, Mg. per 100 Cc. Blood				Postmortem Determinations, Mg. per 100 Cc. Blood			
									Creatinine		Urea		Creatinine		Urea	
			Range	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average
I	Acute infections	15	1 to 24	11.2	9 hr. to 22 days	5 days	65% record in 1 case	65%	1.2 to 2.9	1.8	10.2 to 45.0	21.4	1.7 to 3.6	2.2	19.2 to 65.0	40.1
II	Miscellaneous diseases	51	1 to 24	6.2	3 hr. to 16 wk.	16 days	P.S.P. 40% to 83%	67%	1.1 to 4.2	1.6	9 to 83	20.1	1.4 to 3.3	2.3	11.4 to 98.5	35.3
III	Intestinal obstruction	4	3 to 9	6.5	5 to 12 days	6.5 days	None done	....	1.3 to 2.5	1.8	12.6 to 31.2	18.0	2.9 to 3.8	3.3	32.8 to 52.1	46.2
IV	Renal diseases with postmortem creatinine determinations of less than 4 mg.	16	1 to 15	4.8	1 hr. to 30 days	12.6 days	None done	....	1.2 to 3.1	1.9	11.4 to 71.4	29.6	1.7 to 3.7	2.6	12.6 to 83.8	52.4
V	Renal diseases with postmortem creatinine determinations of 4 or more mg.	14	½ to 15	4.9	2 to 150 days	16 days	P.S.P. traces in 4 cases; diazo test* on blood positive in 2 cases antemortem and 2 cases postmortem		3 to 10.0	5.6	32 to 125	59.6	4.1 to 12	7.3	50 to 192	96.9

* Polayes, S. H.; Lederer, M., and Fradkin, W. Z.: Observations on the Diazo Test in Nephritis, J. Lab. & Clin. Med. **14**: 229, 1928.

Autopsies were performed in 40 per cent of the cases. Those showing gross or microscopic evidences of renal changes were placed in the renal disease groups regardless of the blood determinations.

ANALYSIS OF DATA

Urea.—It will be noted from table 1 that the greatest blood urea content occurred post mortem in the disease group showing the highest blood creatinine values at autopsy, namely, in the group of renal diseases, in which average creatinine values of 5.6 were obtained ante mortem. Next in order follow the other group of renal diseases, intestinal obstruction, acute infections and the miscellaneous group. Great differences were noted, however, between the urea nitrogen determinations on the blood specimens obtained before and after death. It at once became apparent, therefore, that postmortem determinations of urea would be of no value as an aid in determining the degree of retention during life. Thus, case 15 showed 55.5 mg. of urea per hundred cubic centimeters of blood post mortem as compared to 15.5 mg. six days prior to death. Similarly, case 49 with a urea reading of 11.4 mg. twelve days before death showed a postmortem determination of 62.5 mg. Similar examples were found in thirty-four other cases. The reverse was also found to be true. In six cases, the urea values during life exceeded those obtained on postmortem examination. Thus, in case 24, the postmortem determination of urea showed 34.5 mg. per hundred cubic centimeters of blood, while the values obtained two days before death were 83.3 mg. These observations show the unreliability of postmortem determinations of urea as an index of the urea content of the blood ante mortem.

The determination of an arbitrary figure above which all cases are to be considered as falling into the group of renal insufficiency (as will be described with creatinine) is also impossible. This is true because higher urea figures have been found in some cases that presented no evidence of renal disease clinically or anatomically than were found in some frank cases of uremia.

Creatinine.—A study of table 1 shows that postmortem there is an average rise in the creatinine figures of from 0.5 to 1.7 mg. over those which were obtained during life. The lowest average postmortem figures (2.2 mg.) were obtained in the group of acute infections; the highest (7.3 mg.), in the group of renal diseases. Blood specimens from patients with intestinal obstruction yielded average creatinine figures (3.3 mg.) that were higher than those obtained from the miscellaneous group (2.3 mg.). They were even higher than those found in the first group of renal diseases (2.6 mg.).

TABLE 2.—*Renal Diseases with Postmortem Creatinine Figures of Four or More Milligrams per Hundred Cubic Centimeters of Blood*

Case	Diagnosis	Autopsy	No. of Hours Postmortem Specimen Was Received	Interval Between Antemortem and Postmortem Determinations	Renal Function Tests and Other Tests Indicating Renal Status	Creatinine in Mg. per 100 Cc. of Blood	
						Antemortem	Postmortem
6	Acute nephritis, uremia	Yes	1	6 hours	.....	5.0	5.0
15	Verrucose endocarditis amyloid degeneration of kidneys; thrombosis of left renal vein	Yes	2	6 days	.....	5.0	7.8
17	Uremia.....	No	1	4 days	Positive diazo reaction on the blood post mortem	6.0	6.0
22	Chronic glomerular nephritis	Yes	2	5 mo.	No creatinine determination was made later than 5 months before death, but a chemical analysis made 1 month before death showed the following: total nitrogen, 1.26 Gm.; total protein, 5.52%; nonprotein nitrogen, 377 mg.; the blood diazo test ante mortem was also positive; the phenolsulphonphthalein was 14% a year before death	3.0	7.5
23	Acute, subacute and chronic glomerulonephritis, with terminal uremia	Yes	2	10 days	Phenolsulphonphthalein test showed faint traces of the dye	6.0	10.0
32	Hypertension; chronic nephritis	Yes	3	30 days	Phenolsulphonphthalein test showed traces of the dye	3.0	4.1
45	Pyelonephrosis nephrotomy; uremia	No	8	4 days	Phenolsulphonphthalein test showed faint traces of the dye	6.0	4.2
58	Arteriolar sclerosis of kidney uremia	Yes	3	4 days	Blood diazo positive ante mortem	7.1	9.4
71	Pyonephrosis	No	8	4 days	.....	3.3	6.0
83	Pyonephritis	Yes	5	2 days	Phenolsulphonphthalein test, 11%	7.0	9.1
84	Cirrhosis of liver; chronic nephritis; uremia	No	6	2 days	Blood diazo positive ante mortem	5.0	7.0
86	Malignant nephrosclerosis; hypertension; uremia	No	4	4 days	Blood diazo positive nine days before death	10.0	10.0
98	Malignant nephrosclerosis; hypertension; uremia	No	15	5 days	.....	5.0	5.2
99	Mercuric chloride poisoning; acute and subacute nephritis	Yes	12	8 days	Blood diazo positive six days before death	8.5	12.0

A study of table 2 shows that readings of 4 mg. or more per hundred cubic centimeters of blood were found only in cases of renal insufficiency as determined clinically at autopsy and by the other renal function tests mentioned. Furthermore, when the creatinine content post mortem was 4 mg. or over, the figures obtained during life were over 3 mg., which is universally accepted as definite evidence of severe impairment of renal function. Thus, in the group of renal diseases previously tabulated, which yielded postmortem figures for creatinine ranging between 4.1 and 12 mg. (average 7.3 mg.), the values during life ranged between 3 and 10 mg. (average 5.6 mg.) No such high figures were obtained ante mortem in any of the other groups, including that group of renal diseases in which the postmortem values were less than 4 mg. per hundred cubic centimeters of blood. Therefore, it may be concluded that although not all cases of renal disease clinically or anatomically show high blood creatinine figures post mortem, the finding of 4 mg. or more per hundred cubic centimeters of blood after death indicates that high figures (3 mg. or more) existed during life, and that there must have been a condition of severe renal insufficiency.

COMMENTS ON GROUPS OF TABLE 1

I. Autopsies were performed in six cases of this group. The conditions in these cases included lobar pneumonia and bronchopneumonia, meningococcic meningitis, agranulocytic angina, bacterial endocarditis and bacteremia.

II. Autopsies were performed in sixteen cases of this group. The 4.2 mg. of creatinine noted occurred in only one case. This case was one of syphilitic endocarditis, and no evidence of renal dysfunction was found. The next highest reading was 2.9 mg.

III. Autopsies were performed in two cases of this group; neither revealed any renal disease.

IV. Autopsies were performed in eight cases of this group, and renal disease was found in all. Neoplastic thrombi in large renal vessels with infarctions were found in two cases, pyonephrosis in two and arteriosclerosis in three. The rest gave clinical evidence of renal disease but showed no nonprotein nitrogen retention in the blood.

V. Autopsies were performed in eight cases of this group. Three of these showed severe acute or chronic glomerulonephritis; one showed pyonephritis; one, thrombosis of the main renal vein; one, severe arteriosclerotic kidneys, and one, mercuric chloride poisoning. The remaining six cases were all clinically classic cases of severe renal insufficiency in which death was due to uremia.

CONCLUSIONS

From a postmortem study of the creatinine and urea contents of the blood specimens in 100 cases, the following conclusions may be made:

1. Blood creatinine determinations are often helpful as an aid in determining the status of the renal function during life.

2. The urea values are not as helpful as the creatinine figures.

3. A creatinine content of 4 mg. or more per hundred cubic centimeter of blood obtained post mortem indicates marked creatinine retention during life and therefore severe renal insufficiency.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

I. CONCENTRATION OF NONPROTEIN NITROGENOUS CONSTITUENTS IN THE BLOOD *

A. MAURICE WAKEMAN, M.D.
AND
CLARE A. MORRELL, M.A.
NEW HAVEN, CONN.

The work on metabolism in yellow fever which is reported in this and in subsequent articles was carried out from March 15, 1928, to May 6, 1929, for the Yellow Fever Commission of the Rockefeller Foundation at Lagos, Nigeria.

When the work was practically completed, but before it was prepared for publication, Dr. A. Maurice Wakeman contracted an illness which ended fatally before his return to this country. Publication work has, therefore, been carried out entirely by the junior author. In the course of planning the studies and conducting the experiments, Dr. Wakeman had ample occasion to express his views as to the significance of the data obtained and every attempt has been made to present the material in accordance with his views.

It was hoped that there would be human material available for investigation, but by the time the studies were begun, the epidemic of yellow fever in Nigeria had subsided. Stokes, Bauer and Hudson, however, had demonstrated that Indian monkeys, *Macacus rhesus*, were susceptible to the disease; and Hudson [1] has shown that the pathologic lesions produced by the disease in the monkey are quite similar to those which have been demonstrated in human autopsies. The studies were, therefore, conducted entirely on experimentally infected *Macacus rhesus* monkeys, of which an adequate supply was available. Because in both human beings and monkeys the major pathologic lesions of the disease have been found in the liver, greater attention was given to the study of those chemical and metabolic functions which are known to be influenced mainly by the liver. However, attention was not entirely diverted from other functions and those of the kidney were especially noted.

* Submitted for publication, Jan. 30, 1930.

* From the laboratory of the West African Yellow Fever Commission of the International Health Division, Rockefeller Foundation, Lagos, Nigeria.

1. Hudson, N. P.: Am. J. Path. **4**:395, 1928.

The present paper deals with the nitrogen metabolism and the concentration of nitrogenous substances in the blood during the course of yellow fever. It has been demonstrated that in the terminal stages of the disease, the faculties of deaminizing amino-acids to acid-forming urea, functions which are now known to reside chiefly if not entirely in the liver, are greatly impaired.

The technics employed in the management of monkeys throughout these investigations are described in this article and will be used for reference in subsequent papers of this series.

A search of the literature has revealed no studies of the chemistry and metabolism of yellow fever which are significant. Urinalyses for a variety of substances were made by Penido [2] but, owing to the absence of any attempt at dietary control, cannot be interpreted.

EXPERIMENTAL METHODS

Treatment of Animals: Diets.—The animals used in these experiments were Indian monkeys, *Macacus rhesus,* weighing between 1.5 and 4 Kg. The heavier animals were selected to facilitate the obtaining of reasonably large quantities of blood. Those that were being used for experimental work were kept in individual cages.

The monkeys were fed in either of two ways. In experiments in which regulation of diet or collection of samples of urine was unnecessary, the usual animal house food was given in three meals a day. Breakfast consisted of one of the following combinations: (1) sugar cane, 45 Gm.; casava, 45 Gm.; (2) sugar, 40 Gm.; tiger nuts, 7 Gm.; corn, 7 Gm.; (3) sugar cane, 50 Gm.; rice, 45 Gm.; water, 100 cc.; or (4) sugar cane, 50 Gm.; tiger nuts, 7 Gm.; peanuts, 7 Gm.; water, 100 cc. Lunch was composed of 20 Gm. of bread and 100 cc. of condensed milk. Supper included 20 Gm. of corn, half of one hard-boiled egg, half an orange, 20 Gm. of peanuts and 100 cc. of water. The food was placed in small metal dishes and thrust into the cages, where the monkeys ate as much of it as they wanted.

For the purpose of regulating the nitrogen and carbohydrate intake in the metabolism experiments, a special liquid diet which could be fed by a stomach tube was used. Feeding in this manner eliminated the possibility of contamination of urine and feces with the diet and made it possible to measure and regulate the amount of food given. At first a semisolid mixture containing minced bananas and peanuts was used, but since this combination was extremely difficult to force through the stomach tube, it was abandoned.

Diet no. 1, which was used throughout the experiment with *M. rhesus M 1,* consisted of the following combinations: 600 cc. of unsweetened evaporated milk, 150 cc. of orange juice, 300 Gm. of cane sugar and 4 Gm. of salt (NaCl) made up to 1,220 cc. with water. Analysis of this diet showed it to contain 4.18 Gm. of protein and 0.435 Gm. of chloride (as NaCl) per hundred cubic centimeters. The monkey was fed 60 cc. twice a day, making a total of 210 calories with 810 mg. of nitrogen and 520 mg. of sodium chloride.

2. Penido, J. C. N.: Supplemento das Memorias Instituto Oswaldo Cruz, Febre Amarella, no. 2, 1928, p. 65.

In view of the positive nitrogen balance which persisted throughout the normal period in *M. rhesus* M 1, it was concluded that this diet contained more nitrogen than the animal had received in the regular diet.

Diet no. 2 was designed to reduce the protein intake. It consisted of the following ingredients: evaporated milk, 400 cc.; orange juice, 150 cc.; cane sugar, 350 Gm.; sodium chloride, 4 Gm., made up to 1,220 cc. with water. Animals were fed 60 cc. of this combination morning and night, the total containing 530 mg. of nitrogen and yielding 202 calories.

Diet no. 3 was made to reduce the nitrogen intake still further. It was made as follows: evaporated milk, 300 cc.; orange juice, 150 cc.; cane sugar, 300 Gm.; sodium chloride, 4 Gm., made up to 1,100 cc. with water; 120 cc. of this diet yielded 447 mg. of nitrogen and 200 calories.

When it was desired to study changes occurring in the urine during the course of the disease, the animals were fed on one of these diets, the urine and stools were analyzed and periodic blood studies were made.

Special cages were constructed which made it possible to collect all of the urine and feces. The cage consisted of wooden framework, 3 feet wide, 3 feet long and 2 feet high, covered with a wire grating and supported by four legs about 14 inches above the ground. One side opened as a door. It was provided with a movable wire grating on which the monkey rested and which caught the feces. Immediately below this was a pyramidal tin tray which caught the urine. This was also removable and, with the grating, could be slid in or out in grooves directly below the cage door. There was a small spout in the bottom of the tray to which a wide mouthed 100 cc. bottle was attached by means of a rubber stopper. The whole cage was made mosquito-proof by covering it with 20-gage copper wire netting.

Monkeys to be used in metabolism experiments were transferred from the runways to these cages and fed on standard diet from five days to several weeks before studies were commenced. This preliminary period served to establish the monkeys on a more or less constant nitrogen excretion and to accustom them to the diet and handling. Any animal that developed diarrhea was at once discarded. The care of the animals, feeding, cleaning and collecting excrement, was carried out by native boys under our supervision.

Collection of Excreta.—The daily routine commenced at 8 a. m. At that hour the monkey was induced to void any urine which happened to be in the bladder. This could be done almost every time by simply catching hold of the monkey. The bottle containing the specimen was then replaced by a fresh one. The bottle with the morning urine was labeled, stoppered and placed on ice to be analyzed as part of the preceding twenty-four hour excretion. The monkeys were then removed from the cage. After the rectal temperature had been recorded and the monkeys' fur brushed thoroughly to remove any loose hair or dandruff, they were fed the special diet by stomach tube. The procedure of feeding was carried out by thrusting a wooden gag with a hole in the center between the teeth and gently forcing a small soft rubber catheter down the esophagus. A 100 cc. syringe containing the measured quantity of the diet was attached to the catheter. The weight of the plunger was sufficient to force the liquid into the stomach. In monkeys which came to autopsy after long periods of forced feeding, no erosion of the esophagus or stomach was observed. At 8 a. m. and 5 p. m., the collection tray was washed with about 40 cc. of distilled water and the washing collected in a separate bottle. The 8 a. m. washing was analyzed with the urine obtained the previous day. At 5 p. m., the monkey was removed from the cage, fed and brushed, and the temperature taken as before. This time, after the tray

had been washed with distilled water, it was taken out, thoroughly scrubbed with a brush, first with tap water and then with distilled water, and afterward dried.

The urine was divided into two classes; that excreted from 8 a. m. to 8 p. m. was labeled day urine and that from 8 p. m. to 8 a. m., night urine. The bottles were removed after each voiding, marked, stoppered and put on ice to await analysis. A few drops of toluene were added to each bottle before it was attached to the collection tray. The animal was offered additional water at 12 o'clock noon, and the amount drunk was recorded.

The accuracy with which the total amount of nitrogen excreted could be recovered by this method of collection and washing was checked. An artificial urine solution was made which contained a known quantity of urea and ammonium sulphate. Quantities amounting to 50 cc. of this solution, containing 84.4 mg. of nitrogen, were sprayed over a collection tray at three hour intervals for ten hours. Only 37 cc. of the 50 cc. of liquid was recovered immediately. The tray was washed with 50 cc. of water and the artificial urine and washings made up to 100 cc. This was analyzed for total nitrogen content by the macro-Kjeldahl method. In one experiment an average of 86.4 mg. of nitrogen was recovered. In another experiment in which the collection extended over twenty-four hours, an average of 83.1 mg. of nitrogen was found.

In the course of the metabolism experiments with two monkeys, several months after this routine for collecting urine was established, it was found that little or no urea nitrogen could be recovered from their urine while the ammonia nitrogen had greatly increased. Only after washing the cages thoroughly with lye and a compound solution of cresol did the amount of urea and ammonia nitrogen excreted return to a normal level. It was evident that the urine had been contaminated with some organism capable of converting the urea nitrogen to ammonia, in spite of the presence of toluene.

At the conclusion of the twenty-four hour period, the various bottles of day urine were mixed, and the volume and the reaction to litmus were noted. The night urine was treated in a similar way. The individual collecting bottles were rinsed with wash water and the rinsings added to the urine. The day and night urines were combined and mixed thoroughly. After the volume had been recorded, the urine was filtered to remove any hair or dirt which might have collected on the tray of the cage. The residue was usually very small, and was analyzed on several occasions for nitrogen. The average nitrogen content of four such residues was 3 mg.

In one case it was attempted to mark off the stool periods by giving powdered charcoal with the morning feeding. This method proved unsatisfactory, since the charcoal appeared in the feces about thirty-six hours later and continued to be excreted for several days. After this, whatever was excreted during the day was collected and transferred to a bottle containing a weighed quantity of concentrated sulphuric acid. The stool periods were commenced and ended twenty-four hours after the urine periods. The bottle containing the excrement for a period was thoroughly mixed by shaking and an aliquot analyzed for total nitrogen by the macro-Kjeldahl technic. The total amount of nitrogen was calculated and divided by the number of days in the period to give the daily excretion. As a rule, the animals had two formed stools a day, of putty-like consistency, yellowish brown, an inch long and about the diameter of a lead pencil.

The metabolism studies were divided, for the purpose of comparison, into a preliminary period during which complete analyses were not made; a normal control period; a yellow fever period, and, in the case of the animals which recovered from the disease, a recovery period. The lengths of the periods were

regulated by the temperature chart, the time of infection and the clinical appearance of the monkeys.

Collection and Analyses of Blood.—Blood samples were collected from the saphenous vein in the leg, from an arm vein, or from the heart. Since cardiac punctures were liable to cause hemopericardium, resulting in the death of the animal, this technic was never used if it could be avoided. When large amounts of blood were taken, the femoral artery or vein was exposed under local anesthesia. Experience proved that a vein in the arm was the most satisfactory to use in drawing moderate amounts of blood. From 5 to 10 cc. of blood could usually be obtained from this vessel. During the last hours of life, it was often extremely difficult to obtain more than 1 cc. of blood from any vein. This appeared to be due to the pronounced fall in blood pressure which accompanied the prostration of the animal. In these cases cardiac puncture was resorted to.

In drawing blood from the arteries during yellow fever, special precautions against spurters were taken. A framework with a glass top was placed over the animal, and the manipulations were carried out under this. The glass presented an effective screen against blood being thrown up into the face, without hiding the field of operation. In handling all virulent material, rubber gloves were worn and supplemented during more complicated operative procedures with rubber sleeves and apron. Blood used for nitrogen determinations was collected in a clean dry syringe, transferred to a small flask and shaken with a few milligrams of lithium oxalate to prevent clotting. About 1 mg. of lithium oxalate per cubic centimeter of blood was used. For electrolyte studies, the blood was collected in a syringe under mineral oil and the serum separated with anaerobic precautions by the technic of Austin and his co-workers.[3]

Analytical Methods.—The proteins of the blood were precipitated by the tungstic acid method of Folin and Wu.[4] The nonprotein nitrogen was determined by Folin's micro-Kjeldahl digestion followed by direct nesslerization of the digestion mixture.[5] Amino-acid nitrogen was estimated by the colorimetric method of Folin.[6] The uric acid values were obtained by Folin's direct method,[7] with Folin and Trimble's phosphotungstic acid reagent.[8] Folin's method[9] for creatinine was employed, with pure creatinine as the standard and trinitrophenol purified according to the technic of Folin and Doisy.[10] Ergothioneine was determined by Hunter's[11] method. Ammonia was estimated by Folin's technic.[12] Benedict's[13] method for blood sugar was used. Phosphorus was determined by the method described by Fiske and Subbarow,[14] and chlorides by the method of van Slyke.[15] Bile pigments were estimated by the van den Bergh technic.[16]

3. Austin, J. H.; Cullen, G.; Hastings, A. B.; McLean, F. C.; Peters, J. P., and Van Slyke, D. D.: J. Biol. Chem. **54**:121, 1922.
4. Folin, O., and Wu, H.: J. Biol. Chem. **38**:81, 1919.
5. Folin, O., and Wu, H.: J. Biol. Chem. **38**:90, 1919.
6. Folin, O.: J. Biol. Chem. **51**:377, 1922.
7. Folin, O.: J. Biol. Chem. **54**:153, 1922.
8. Folin, O., and Trimble, H. C.: J. Biol. Chem. **60**:473, 1924.
9. Folin, O., and Wu, H.: J. Biol. Chem. **38**:98, 1919.
10. Folin, O., and Doisy, E. A.: J. Biol. Chem. **28**:349, 1917.
11. Hunter, C.: Biochem. J. **22**:4, 1928.
12. Folin, O., and Denis, W.: J. Biol. Chem. **11**:534, 1912.
13. Benedict, S. R.: J. Biol. Chem. **68**:759, 1926.
14. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.
15. Van Slyke, D. D.: J. Biol. Chem. **58**:523, 1923.
16. McNee, J.: Quart. J. Med. **16**:390, 1923.

Urea nitrogen in the blood was in some cases estimated by hydrolysis with urease, aeration of the ammonia into standard acid and nesslerization. Owing to a very uncertain air current this method proved unsatisfactory, and in the absence of any source of heat for distillation which could be regulated the following procedure was adopted: Ten cubic centimeters of the blood filtrate was transferred to a 50 cc. volumetric flask which had been rinsed first with 10 per cent nitric acid and distilled water. After the addition of 1 cc. of a freshly prepared 10 per cent solution of Squibb's urease powder, the mixture was allowed to stand at room temperature (30 to 35 C.) for twenty minutes. One and a half cubic centimeters of washed, dust-free permutit powder was added from a graduated 15 cc. centrifuge tube, after having been tapped down to the mark. The flask was agitated gently for five minutes and the permutit powder washed by decantation with 100 cc. of distilled water; 10 cc. of water and 0.5 cc. of 10 per cent sodium hydroxide were then added, followed by enough water to bring the volume to about 40 cc. After the addition of 5 cc. of Nessler's solution the whole was made up to volume. The standard was prepared as follows: Into a 100 cc. volumetric flask which had been washed with nitric acid and water, 20 cc. of distilled water was introduced, followed by 2 cc. of the urease solution. After the solution had stood twenty minutes, 3 cc. of the permutit powder was dropped in and the flask agitated gently for five minutes. After washing and the addition of a double quantity of water, 1 cc. of 10 per cent sodium hydroxide was run in, followed by 3 cc. of a standard ammonium sulphate solution containing 0.1 mg. of nitrogen per cubic centimeter. The solution was diluted to 80 cc. with water, 10 cc. of alkaline potassium mercuric iodide test solution (Nessler's reagent) poured in, and the whole brought up to volume. Standards and blood filtrates were treated simultaneously.

Analysis of Urine.—Urine was analyzed for total nitrogen by Folin's method of direct nesslerization[17] and, when the quantity permitted, this method was checked by macro-Kjeldahl digestion and titration with 0.05 normal acid and alkali. Amino-acid nitrogen was determined by the colorimetric procedure of Folin[18] and ammonia by the method of Folin and Bell.[19]

For uric acid, the precipitation technic of Folin and Wu[20] was used. Creatinine was determined by the method of Folin[21] and phosphorus by that of Fiske and Subbarow;[14] chlorides were estimated by the Volhard-Harvey[22] procedure, and organic acid by the titration described by Van Slyke and Palmer.[23]

The protein was estimated in some cases by means of an albuminometer and Esbach's reagent, and in others by determining total nitrogen before and after precipitating the protein with tungstic acid, and multiplying the difference by 6.25. A solution of sodium nitroprusside was used for qualitatively testing for acetone in a few specimens of urine. The qualitative tests for sugar were performed with Benedict's solution.

Urea was determined by a slight modification of the Folin and Youngburg method,[24] because the original technic often yielded cloudy or greenish colored

17. Folin, O., and Denis, W.: J. Biol. Chem. **26**:473, 1916.
18. Folin, O.: J. Biol. Chem. **51**:393, 1922.
19. Folin, O., and Bell, R. D.: J. Biol. Chem. **29**:329, 1917.
20. Folin, O., and Wu, H.: J. Biol. Chem. **38**:459, 1919.
21. Folin, O.: J. Biol. Chem. **17**:469, 1914.
22. Harvey, S. C.: The Quantitive Determination of the Chlorids in the Urine, Arch. Int. Med. **6**:12 (July) 1910.
23. Van Slyke, D. D., and Palmer, W. W.: J. Biol. Chem. **41**:567, 1920.
24. Folin, O., and Youngburg, G.: J. Biol. Chem. **38**:111, 1919.

solutions on nesslerization. At first an alcoholic extract of jack bean was made, but later this was replaced by Squibb's urease powder. The urease reaction was carried out in a 250 cc. volumetric flask that had been rinsed previously with nitric acid and distilled water. The ammonia nitrogen was either removed beforehand with permutit or both determined together and the ammonia nitrogen subtracted from the total. Enough urine to contain approximately 1 mg. of urea nitrogen was transferred to the flask with 10 cc. of water and 1 cc. of freshly prepared 10 per cent urease solution. After the mixture had stood for twenty minutes at room temperature (30 to 35 C.), 3 cc. of dust-free permutit powder was added. This was measured in a 15 cc. conical graduated centrifuge tube. The tube was tapped on the desk two or three times to shake the powder down to the mark. After the addition of the permutit powder, the flask was swirled for five minutes and the powder washed, by decantation, with about 200 cc. of distilled water; 10 cc. of water and 1 cc. of 10 per cent sodium hydroxide were then run in, the flask was gently agitated from three to five minutes, and the contents made up to 200 cc.; 20 cc. of Nessler's solution was added and the whole made up to volume with water. The standard was treated in precisely the same manner except that an equal quantity of water was used in place of the urine and 1 cc. of an ammonium sulphate solution containing 1 mg. of nitrogen was added after bringing the volume to 200 cc. with water.

The accuracy of this method was tested with standard urea and ammonium sulphate solutions. From 97 to 100 per cent of the theoretical amount of urea nitrogen was recovered.

Clinical Observations.—Clinical manifestations in the *rhesus* monkeys infected with yellow fever virus have been described by Stokes, Bauer and Hudson.[25] A brief résumé with a few additional remarks is given here. The animals used in this work were infected with blood virus or liver emulsion or by a mosquito bite. Stokes, Bauer and Hudson found the average incubation period in the monkeys bitten by mosquitoes to be between three and four days, and in those inoculated with blood virus between two and three days. Rectal temperatures were taken twice a day, between 8 and 9 a. m. and 4 and 5 p. m. After a consideration of the normal temperatures of a large number of monkeys, any temperature of 104 F. or over was taken as an indication of fever, an arbitrary standard which was not always satisfactory. Occasional temperatures of 104 F. or more were observed in normal animals. On the other hand, in some monkeys with normal temperatures as low as from 100 to 101 F., the temperature during the course of the disease never rose as high as 104 F.

The course of the fever showed considerable variation in different animals. Some had a very short course while in others fever persisted over a period of a week or more. In some monkeys there was a return to normal or even subnormal temperature after a short period of fever, followed by a terminal rise. In a great many cases, the temperature during the last few hours of life was subnormal.

During the incubation period and usually during the first day of fever, no indications of illness were evident. If the febrile period was short and terminated in the death of the animal from two to three days after the onset of fever, symptoms were usually apparent on the second day. The animals became listless and required greater stimuli to rouse them to activity. On the last day of life they were found lying down and unresponsive to any movement of their cages, giving every appearance of being unconscious of their surroundings.

25. Stokes, A.; Bauer, J. H., and Hudson, N. P.: Am. J. Trop. Med. **8**:103, 1928.

In nineteen cases observed no food was taken for from seven to eighteen hours and, in one case, thirty-six hours before death. In every case the last meal taken was milk or orange juice, the solid part of the diet being refused. Twelve animals were found lying down or prostrated from seven to twenty hours before death; four were feebly sitting up. No observations were made on the remaining three.

The monkeys usually drank water after they had refused all food, in several instances consuming as much as 100 cc. at one time. Three of the monkeys used in the metabolism experiments vomited during the febrile period, and the stomachs of a considerable number at postmortem examination contained quantities of altered blood.

TABLE 1.—*Normal Values for Nonprotein Nitrogenous Constituents of Blood*

	Non-protein Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen	Creatinine	Uric Acid	Rest Nitrogen
Animals on regular diet:						
Number of animals	17	13	14	9	14	12*
Number of observations	17	13	14	9	14	12*
Maximum mg. per cent	54.0	21.9	9.3	1.96	1.80	33.5
Minimum mg. per cent	31.4	9.0	4.8	1.33	0.10	11.3
Average mg. per cent	40.7	15.5	8.12	1.54	0.82	18.0
Nitrogen as per cent total nitrogen:						
Number of animals	....	11	11	9	6	10
Number of observations	....	13	13	9	6	12
Maximum per cent	....	50.0	26.7	1.68	1.24	63.7
Minimum per cent	....	20.4	9.8	1.15	0.31	34.6
Average per cent	....	36.8	19.5	1.38	0.53	43.0
Animals on special diet:						
Number of animals	16	8	12	....	2	6*
Number of observations	20	9	16	....	2	10*
Maximum mg. per cent	52.5	19.7	9.0	....	2.0	0.8
Minimum mg. per cent	25.0	9.8	5.0	....	0.80	7.3
Average mg. per cent	35.6	13.2	7.0	....	1.90	12.2
Nitrogen as per cent total nitrogen:						
Number of animals	....	8	10	....	.....	6
Number of observations	....	9	14	....	.....	10
Maximum per cent	....	51.8	25.8	....	.....	43.4
Minimum per cent	....	31.8	10	....	.....	35.7
Average per cent	....	41.5	19.6	....	.....	35.3

* Where creatinine and uric acid had not been determined an average value was assumed for calculation of the rest nitrogen.

BLOOD STUDIES

A. Normal Animals.—Figures for the nonprotein nitrogenous constituents in the blood of normal monkeys are presented in table 1. The figures have been divided into two groups, those from animals on the regular diet, and those from animals fed on the special diet. All monkeys in the latter group had received the special diets for from five days to two weeks previous to the taking of blood. The most striking difference between the two groups is the higher average level of nitrogenous constituents in the blood of animals on the regular diet. This difference is quite inexplicable as there is reason to believe that the special diets contained more nitrogen than the regular diet. The blood samples in both groups were taken in some cases before feeding and

in others, after feeding. In both groups, the average nonprotein nitrogen is higher than it is usually found to be in normal human blood.

The higher uric acid values observed on the special diet cannot be considered significant since only two animals are included in this group. The relative amounts of urea nitrogen, amino-acid nitrogen and creatinine are in accord with those found in human blood.

Ammonia nitrogen was determined in the blood of two monkeys, and only a trace could be found. The variation between maximum and minimum figures for all the nitrogen constituents was quite large, and there seemed to be no difference between the two groups in this respect.

TABLE 2.—*Values for Nonprotein Nitrogenous Constituents of Blood in the Final States of Yellow Fever*

	Nonprotein Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen	Creatinine	Uric Acid	Rest Nitrogen
Animals on regular diet:						
Number of animals	26	19	22	6	9	19*
Number of observations	33	26	29	6	9	24*
Maximum mg. per cent	128.0	46.5	43.7	2.6	1.5	54.6
Minimum mg. per cent	44.7	10.7	5.5	1.1	0.5	14.8
Average mg. per cent	78.3	27.0	20.9	1.7	0.8	32.2
Nitrogen as per cent total nitrogen:						
Number of animals	.....	16	15	5	5	15*
Number of observations	.....	23	22	5	5	22*
Maximum per cent	.....	47.8	42.2	1.2	0.4	65.4
Minimum per cent	.....	14.8	8.1	0.6	0.2	24.7
Average per cent	.....	35.7	26.6	0.8	0.6	39.1
Animals on special diet:						
Number of animals	5	7	5	2	3	4*
Number of observations	8	10	7	2	3	7*
Maximum mg. per cent	99.0	28.0	32.7	3.0	1.0	60.0
Minimum mg. per cent	50.0	5.3	12.0	2.3	0.5	19.0
Average mg. per cent	68.6	16.0	20.8	2.6	0.7	29.6
Nitrogen as per cent total nitrogen:						
Number of animals	.....	4	4	2	...	4*
Number of observations	.....	6	6	2	...	6*
Maximum per cent	.....	58.0	47.2	2.1	...	61.6
Minimum per cent	.....	5.3	22.0	1.3	...	20.0
Average per cent	.....	23.4	29.5	1.7	...	44.7

* Where creatinine and uric acid had not been determined an average value was assumed for calculation of the rest nitrogen.

B. Analyses of Blood During the Terminal Stages of Yellow Fever.—The results of blood analyses during the terminal stage of yellow fever are presented in table 2. The figures were obtained only from animals that were moribund or obviously very ill. Some of the animals were in the first day of fever while others had undergone a prolonged febrile period. As has been pointed out previously, the duration of the illness is quite variable, and many monkeys are prostrated and die shortly after the onset of fever. It is only after the disease has produced obvious clinical symptoms that the concentrations of the nitrogenous constituents of the blood are appreciably altered. Figures obtained during the earlier stages of the disease have been collected in another table.

Table 2 shows clearly the great increase in nonprotein nitrogen which occurs in these moribund animals. Coincident with this, there is an elevation of the urea nitrogen and amino-acid nitrogen. Creatinine increases but little and uric acid not at all. The proportion of the total nonprotein nitrogen contributed by these two constituents is greatly reduced.

Calculated as per cent of the total nonprotein nitrogen, the urea nitrogen, although increased on the average in absolute amount, shows a decrease from 41.5 to 23.4 per cent in the special diet group and from 36.8 to 35.7 per cent in the regular diet group.

The most significant change occurs in the amino-acid nitrogen which shows strikingly large gains both in absolute amount and in relation to the total nitrogen. From approximately 19.5 per cent of the total nitrogen in both normal groups it has risen to 26.6 and 29.5 per cent. In one monkey on a special diet it formed 47.2 per cent of the nonprotein nitrogen, while another on regular diet showed an absolute value of 43.7 mg. per cent. In only one instance was amino-acid found within the normal range, 5.5 mg. per hundred cubic centimeters. The average increase in both groups is from two and a half to more than three times the normal values.

The absolute concentration of rest nitrogen in both groups is markedly increased, although it does not always form a larger proportion of the total nonprotein nitrogen.

Ammonia nitrogen in both samples of blood from animal no. 8 (table 3) was less than 0.5 mg. per hundred cubic centimeters. Here again can be seen the lower concentration of the constituents in the blood of the animals fed on the special diet.

The notable features of the blood nitrogen at the terminal stage of yellow fever are: (1) high concentration of nonprotein nitrogen; (2) absolute increase in urea concentration which is small in proportion to that of nonprotein nitrogen; (3) an increase of amino-acid nitrogen that is large in proportion to that of nonprotein nitrogen; (4) an increase of rest nitrogen, and (5) the fact that uric acid concentration remains unchanged.

NITROGENOUS CONSTITUENTS OF BLOOD IN THE EARLY STAGES COMPARED WITH THOSE IN THE TERMINAL STAGES OF YELLOW FEVER

In table 3 are presented the results of blood analyses made at intervals during the course of the disease. Two or more blood samples were taken from eight of the animals. The other first samples were drawn during the illness, but before the animals became prostrate, while the last blood was taken either post mortem or when the monkeys were obviously moribund.

TABLE 3.—*The Changes in Blood Nonprotein Nitrogen During the Course of Yellow Fever* *

Monkey Number	Blood Samples	Nonprotein Nitrogen as Mg. per Cent			Nonprotein Nitrogen as per Cent Total Nitrogen					
		Total	Urea	Amino-Acids	Urea	Amino-Acids	Blood Sugar	Date	Time	Comment
2	A	37	12	7	33	20	34	May 29	11:30 a. m.	Second day of fever
	B	78	28	18	36	23	18	May 29	8:30 p. m.	Died during removal of blood
3	A	47	21	6	44	12	...	June 4	.....	Normal
							93	June 8	10:20 a. m.	First day of fever
	B	43	20	5	46	12	...	June 8	5:00 p. m.	First day of fever; animal killed
4	A	45	17	12	37	28	43	Dec. 8	3:00 p. m.	Conscious, but weak
	B	60	21	19	35	32	...	Dec. 8	7:10 p. m.	10 minutes after death
5	A	60	30	14	33	23	86	Dec. 10	10:00 a. m.	After one day of fever; vigorous
	B	128	41	43	32	33	34	Dec. 11	9:00 a. m.	Died during removal of blood
6	A	36	12	8	32	21	102	Dec. 11	9:30 a. m.	After one day of fever; not ill
	B	83	29	25	35	29	41	Dec. 15	10:20 a. m.	After two days of fever; not prostrated
	C	88	33	31	38	35	...	Dec. 15	11:20 a. m.	Five minutes after death
7	A	47	11	16	23	35	...	Dec. 17	4:20 p. m.	After two days of fever; very ill, but not prostrated
	B	57	14	23	25	41	...	Dec. 17	7:30 p. m.	Five minutes after death
8	A	112	46	27	41	24	...	Jan. 6	10:00 a. m.	Starved for 13 days
	B	119	47	32	39	27	...	Jan. 6	11:00 a. m.	Five minutes after death
M2	A	29	13	8	45	27	...	Nov. 24	9:00 a. m.	After one day of fever; bright and lively
	B	55	9	27	16	48	...	Nov. 27	8:00 a. m.	After three days of fever; prostrate
	C	67	11	29	16	43	...	Nov. 27	10:30 a. m.	Five minutes after death
M3	A	43	20	8	46	18	109	May 2	2:00 p. m.	Appears normal; last meal at 9:30 a. m.
	B	61	17	15	28	25	66	May 3	8:10 a. m.	Drowsy, but vigorous; last meal May 2 at 4:30 p. m.
	C	67	15	17	22	25	113	May 3	4:10 p. m.	Lying down, weak and listless; last meal at 9:10 a. m.
	D	99	5	33	5	38	15	May 3	10:15 p. m.	Ten minutes after death
M4	A	24	10	5	42	21	...	Nov. 2	.....	Normal
	B	50	28	12	56	24	...	Nov. 5	11:15 p. m.	Ten minutes after death
M5	..	66	18	15	27	23	...	Sept. 30	6:30 a. m.	Fifteen minutes after death
9	..	28	10	8	36	30	...	Feb. 10	9:00 a. m.	After two days' fever; not definitely ill, recovered
10	..	31	13	7	40	22	...	Feb. 11	10:15 a. m.	After two days' fever; not definitely ill, recovered
11	..	37	..	7	..	19	127	Aug. 22	10:15 a. m.	First day of fever; lively, animal killed

* Sample A from no. 3 was taken before the animal was infected. In numbers 9, 10 and 11 the blood was taken during the febrile period, but before clinical symptoms were evident.

Consideration of the blood sugar values obtained during fasting has been included in the remarks wherever the determinations were made. It is interesting to note the extremely low values for blood sugar obtained from the animals in a moribund condition.

The figures given for monkeys 2, 4, 5, 6, M2 and 7 indicate clearly the magnitude of the changes which occur in the last few hours of life.

The percentage of total nitrogen formed by the urea nitrogen and amino-acid nitrogen, respectively, show definitely that these two products do not increase at comparable rates. In the three animals 4, 5 and 8, the urea nitrogen, while increasing in absolute amount, decreases as the per cent of total nonprotein nitrogen in the time intervening

TABLE 4.—*Postmortem Changes in Some Nonprotein Nitrogenous Constituents of Blood*

Number	Minutes Post Mortem	Nonprotein Nitrogen, Mg., per Cent	Urea Nitrogen, Mg., per Cent	Amino-Acid Nitrogen Mg., per Cent	Uric Acid, Mg., per Cent	Comment
		36.5	....	9.28	....	Taken from right basilic vein at 2:20 p. m.
		37.0	....	9.10	....	Taken from right heart at 2:25 p. m.
		.....	....	.....	....	Animal killed by blow on neck at 2:30 p. m.
	15	40.0	....	11.15	....	Taken from right heart at 2:45 p. m.
M8		98.5	51.0	7.6	0.53	Taken from left heart at 2:35 p. m.
	5	100.0	....	7.9	0.52	Animal killed by blow on neck at 2:38 p. m.
		.....	....	.....	....	Taken from left heart at 2:43 p. m. (heart beating)
	14	98.5	49.0	8.5	0.57	Taken from left heart at 2:52 p. m.
		44.1	17.4	8.5	0.45	Taken from right heart at 8:33 a. m.
		.....	....	.....	....	Animal killed by blow on neck at 8:34 a. m.
	5	46.2	17.6	10.1	1.05	Taken from left heart at 8:41 a. m.
	15	50.0	....	11.6	2.50	Taken from left and right heart at 8:49 a. m.
M7		72.3	39.7	8.7	1.25	Taken from right heart at 8:25 a. m.
		.....	....	.....	....	Animal killed by blow on neck at 8:28 a. m.
	6	71.0	36.4	9.3	1.57	Taken from left heart at 8:34 a. m.
	14	71.5	36.4	10.1	1.76	Taken from left heart at 8:42 a. m.

between the two analyses. Both absolute and relative concentrations of amino-acid nitrogen, on the other hand, always increase greatly.

Values given for blood samples 2A, 3B, M2A, 6A, 9, 10 and 11, though obtained from monkeys during the febrile period (in the case of 2A just nine hours before death), lie within the normal range.

Postmortem Changes in Some Nitrogenous Constituents of Blood.—Since many of the terminal blood samples were taken a few minutes post mortem, the question arose if part, at least, of the change observed in the nitrogenous metabolites was not a postmortem change.

In these experiments monkeys which had not been infected were used. Blood was analyzed immediately before death and at intervals up to fifteen minutes after death. The animals were killed in a way that would least affect the blood concentration.

The series of analyses recorded in table 4 indicates that there is in some cases an increase in nonprotein nitrogen in the blood which

remains in the animal from five to fifteen minutes after death. At the same time, the amino-acid nitrogen increased by 3.1 mg. and the uric acid by the usually large figure of 2.05 mg. or almost 0.7 mg. of nitrogen. The nonprotein nitrogen did not always increase, but amino-acid nitrogen and uric acid invariably rose slightly. Urea, on the other hand, decreased somewhat.

Part of these differences may be due to analytical error or incomplete mixing of the blood samples as taken from the heart; but the consistent positive tendency shown by most of them indicates undoubtedly that appreciable autolysis has already occurred. However, it was felt that the differences were negligible when compared with the large increases noted in the animals dying of yellow fever.

Monkeys M6 and M7 had both received injections of uric acid in connection with other experiments; M6 six days previously and M7 nine days previously. We have noticed a marked fall of nitrogen excretion after intravenous or subcutaneous injection of uric acid. In some cases the monkeys become practically anuric for a day afterward, and urinary nitrogen returns to the normal level only after five or six days. This nitrogen retention would account for the high concentration in the blood of M6 and M7.

COMMENT

The most consistent pathologic changes in yellow fever are seen in the liver; the kidneys show degenerative changes in a less marked degree; minor alterations are found in the heart and the spleen. Because the liver presents the gravest lesions, amounting, in the most severe cases, to almost complete destruction of the parenchyma of the organ, one would expect changes in metabolism similar to those found after hepatectomy, namely, a loss of ability to deaminize and to form urea, deficient destruction of uric acid and impairment of hepatic glycogen formation.

A study of carbohydrate metabolism during the disease will be published separately. The results of experiments on uric acid reported in this and the succeeding paper have been supplemented by a more complete investigation which will also be presented separately.

In yellow fever no significant change was found in the uric acid concentration of the blood (tables 1 and 2). This is strangely at variance with the results of Mann and his associates,[26] who reported definite rises of uric acid in the blood of the dog within a few minutes after complete hepatectomy. In the rabbit McMaster and Drury[27]

26. Mann, F. C.: Modified Physiologic Processes Following Total Removal of Liver, J. A. M. A. **85**:1472 (Nov. 7) 1925. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Am. J. Physiol. **72**:629, 1925.

27. McMaster, P. D., and Drury, D. R.: J. Exper. Med. **49**:745, 1929.

have observed similar increases after the removal of 80 per cent of the liver. Mann found that blood uric acid in the dog increased roughly in proportion to the extent of liver destruction and was affected long before disturbances of urea formation or hypoglycemia appeared. In yellow fever, monkeys that died with blood sugars as low as from 14 to 28 mg. per hundred cubic centimeters had only traces, or at the most 1 mg. of uric acid per hundred cubic centimeters of blood. Either uricolysis in the monkey is not so easily disturbed as it is in the dog or the rabbit, or it is a function which is not confined entirely to the liver. That species differences with respect to uricolysis exist is suggested by Rabinowitch's [28] recent report on a case of acute yellow atrophy. This patient exhibited complete absence of deaminizing powers and extreme hypoglycemia without hyperuricacidemia.

Ergothioneine determinations on the blood of three normal monkeys and three monkeys having yellow fever gave entirely negative results. No red color developed on the addition of the tenth-normal sodium hydroxide and no purplish precipitate appeared even after several hours' standing. Furthermore, the blood of two of the normal monkeys, analyzed by Folin's direct method, was found to contain the equivalent of only 0.89 and 0.63 mg. per cent of uric acid, respectively. One of the animals had received the special diet no. 3; the remainder received the regular diet.

Blood creatinine is slightly increased during the terminal stage of yellow fever (tables 1 and 2), probably as a result of the anuria which frequently occurs shortly before death. The increases are not, however, of the magnitude that one would expect if renal insufficiency was an important feature in the course of the disease.

Only traces of ammonia nitrogen were present in the blood of normal monkeys. In the blood of monkey 1 (A and B, table 3) 0.5 mg. per hundred cubic centimeters and in the bloods of two other animals only traces were found in the premortal stages of the disease.

Alterations in the amounts and proportions of the urea and amino-acid nitrogen fractions of the blood in yellow fever are suggestive of loss of liver function. These changes, however, appear only as a terminal event. On the average in the last stages of the disease, urea nitrogen made up a smaller proportion and amino-acid nitrogen a larger proportion of the nonprotein nitrogen than normal (tables 1 and 2).

Blood amino-acid nitrogen increased to a remarkable degree not only in relation to total nonprotein nitrogen, but also in absolute amount. In only one case was it found within normal limits in an animal that had died of yellow fever. On the other hand, the changes in blood urea nitrogen were less consistent. In a large proportion of the cases it

28. Rabinowitch, I. M.: J. Biol. Chem. **83**:333, 1929.

actually increased, although the increases were small in comparison with those of total nonprotein and amino-acid nitrogen. In many instances it remained within normal limits. In a few cases it diminished absolutely. In M2 (table 3) there was a definite decrease in blood urea, and in M3 an even more striking loss. In the latter case the disappearance of urea from the blood, which occurred between 4:10 p. m. and post mortem, cannot be accounted for by excretion in the urine, since no urine was passed after 3 p. m. and none was found in the bladder at autopsy. Bollman, Mann and Magath,[29] in their hepatectomized dogs, in a few instances recorded appreciable reductions of blood urea nitrogen. Rabinowitch [28] found no urea in the blood of a patient with acute yellow atrophy, although only a negligible amount was recovered in the urine. This loss is quite unaccountable, if urea is at all times evenly distributed throughout the tissues, unless it can be utilized or destroyed in some manner by the organism.

The rest nitrogen increased considerably in absolute amount, but not always in proportion to the total nonprotein nitrogen. In animals fed on the regular diet, the average rest nitrogen made up a larger percentage of the total nonprotein nitrogen during the control than it did in the yellow fever period (tables 1 and 2), while in animals receiving special diets the reverse was true.

On the whole then, the blood nonprotein nitrogen and its various components appear to suffer little change during the course of the disease until the premortal period. At this time the observed changes are consistent with, but not entirely characteristic of, the picture which is recognized as the result of total or subtotal ablation of liver function. The complete absence of hyperuricacidemia is out of keeping with the results of experimental investigations on dogs and rabbits. However, as has been pointed out, in at least one human being with maximum liver destruction, blood uric acid was found normal. Species variations in the mode of utilization (and, presumably, oxidation) of purine end-products have long been recognized. Although in its normally low excretion of uric acid the monkey appears more nearly akin to dog than man, in the site of uricolysis he may resemble more closely the human being.

The results of these investigations do not permit the conclusion that the power to form urea from amino-acids invariably suffers; they suggest that in most instances it is greatly impaired before death and in some, completely destroyed. As it seems to be well established that in all animals thus far investigated (dog, rabbit and man) this function is peculiarly confined to the liver, it appears justifiable to conclude that

29. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Am. J. Physiol. **78**:258, 1926.

this organ suffers extreme functional injury in yellow fever and that this injury is responsible for the most important disturbances of the blood nonprotein nitrogen.

The rapid terminal rise of blood nonprotein nitrogen and most of its components may be, and probably is, referable to failure of renal function. It is less certain that this failure can be attributed to any specific pathologic changes in the kidneys. It was most striking in animals that developed complete or almost complete anuria, a not uncommon occurrence during the last day of life. The decrease in both urine volume and excretion of nitrogenous metabolites may well have been associated with a fall of blood pressure which usually preceded death. The blood pressure of the normal *Macacus rhesus*, measured directly by inserting a needle connected to a special manometer into the femoral artery, is approximately 120 mm. of mercury, systolic; 60 mm. of mercury, diastolic. In three monkeys, in the prostration characteristic of the last stages of yellow fever, systolic pressures were found to lie between 50 and 60 mm., diastolic between 40 and 50. This low blood pressure often made it difficult to secure blood from moribund monkeys.

SUMMARY

Determinations of total nonprotein nitrogen and the individual nonprotein nitrogenous components (urea, amino-acid, ammonia, uric acid and creatinine) have been made on the blood of normal *Macacus rhesus* monkeys and similar animals with experimentally produced yellow fever.

Uric acid, creatinine, rest nitrogen and ammonia are not constantly altered, although creatinine and rest nitrogen usually rise to a variable extent in the terminal stages of the disease.

The constituents which are chiefly affected are urea and amino-acids. Amino-acid nitrogen rises rapidly in the terminal stages of the disease; urea nitrogen may rise, but sometimes remains constant or falls. In any case amino-acid increases proportionately far more and urea far less than total nonprotein nitrogen, evidence that the power of the liver to deaminize amino-acids and to produce urea is greatly impaired or destroyed. This functional derangement becomes apparent only during the last hours of life.

FATAL HUMAN ANAPHYLACTIC SHOCK

REPORT OF A CASE, WITH AUTOPSY OBSERVATIONS AND REVIEW OF THE LITERATURE *

JESSE G. M. BULLOWA, M.D.
AND
MENDEL JACOBI, M.D.
NEW YORK

Complications following serum therapy are relatively uncommon. Still more uncommon are reported fatalities. Park [1] estimated that such fatal reactions occur once in 70,000 cases.

Of the pathologic anatomy in cases of fatal anaphylactic shock, little has appeared in the literature. Lamson,[2] in 1924, was able to collect forty cases of sudden death following the injection of serum; twelve of these cases came to autopsy. Since then, one additional case with necropsy observations has been published. Recently a case in the service of one of us (J. G. M. B.) ended fatally; at necropsy changes were presented so similar to those found in experimental anaphylactic shock as to be worth recording.

REPORT OF CASE

History.—C. S., aged 8, was first admitted to the Willard Parker Hospital on Oct. 4, 1928, with a history of cough, "running nose and eyes," and some fever for one week. On admission, she had a marked conjunctivitis, definite Koplik spots on the buccal mucosae and at nction of the hard and soft palate, a mucopurulent nasal discharge and a aculopapules on her face. Schick and Dick tests performed in the admitti oom were negative. Within twelve hours after admission, a marked pruritic rticarial eruption developed on her chin, wrists, abdomen and left foot, which disappeared shortly after epinephrine had been administered. On October 6, a generalized maculopapular rash developed on her face and trunk, which faded in four days. She was discharged on October 13 as recovered from her attack of measles.

She was again admitted to the hospital on November 1, with a history of general malaise, some fever and sore throat which had lasted four days. On admission, she appeared moderately toxic. Considerable mucopurulent discharge was present from the left nostril. A small piece of grumous, greenish membrane

* Submitted for publication, Dec. 24, 1929.

* From the medical and pathological services of the Willard Parker Hospital for Contagious Diseases, New York, and the pathologic laboratory of the Brownsville-East New York Hospital, Brooklyn.

1. Park, W. H.: Tr. A. Am. Phys. **28**:95, 1913; Antitoxin in Diphtheria, J. A. M. A. **76**:109 (Jan. 8) 1921.

2. Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substance, J. A. M. A. **82**:1096 (April 5) 1924.

was present beneath the left inferior turbinate and on the left tonsil. There was moderate edema of the neck. The pharynx was somewhat reddened and granular. The heart sounds showed the first sound to be of poor quality. The scratch skin test for horse serum sensitivity showed no reaction in a few minutes.

The patient was given 5,000 units of diphtheria antitoxin intravenously. She was turned on her side preparatory to receiving an additional intramuscular injection of antitoxin. She complained of being nauseated, and began to vomit. The most marked feature was the very great inspiratory effort in which all the accessory muscles participated, apparently without expansion of the chest, as if a foreign body were present. The chest continued to be small in spite of the obvious expansion of the free border of the ribs and the tugging of the sternomastoids. On auscultation, very little air was heard to enter the chest. The facial muscles were contracted. The contorted face betokened terror.

Epinephrine was given intravenously. Laryngoscopy and bronchoscopy were performed. The trachea was seen to be narrow. Oxygen was administered through the bronchoscope, but very little air seemed to enter the lung. Mouth to mouth insufflation was employed with the hope of increasing the carbon dioxide content and therefore the depths of the inspirations and possible ultimate relaxation of the musculature. Atropine was administered. Gradually, the heart became more irregular, and finally ceased to beat. Respirations became more and more apneustic, later with prolonged expiration, finally gasping, until they ceased several minutes before the heart had stopped.

Autopsy.—Autopsy was performed seven hours postmortem by one of us (M. J.). The body was that of a well developed and nourished white girl whose upper and lower extremities especially were mottled with fine and larger dull, crimson-bluish areas separated by pallid white blotches. The abdomen and face were quite pallid; the buttocks, back and shoulders showed large, blotchy livid areas. The vessels of the dura, sinuses and brain surface were markedly distended with dark, fluid blood. The jugular veins were similarly markedly distended with large amounts of fluid blood. The abdominal veins, notably the portal, both renals and the inferior vena cava were only moderately filled with fluid blood; the mesenteric, splenic and iliac veins were prominent but not unusually distended. No thrombi were found in any vessel.

The turbinates, the nasal septum and nasopharynx were covered by patches of dirty grayish green, blood-tinged exudate confluent over the nasopharynx into a distinct membrane. Beneath this firmly adherent exudate, the mucosa was a deep red, dull and ulcerated; the intervening mucosa was markedly reddened and dulled. On the left tonsil were shreds of firmly adherent fibrinonecrotic, blood-tinged exudate.

When the chest was opened, the heart was seen to be tremendously increased in size. The parietal pericardium, transparent and glistening, was tightly stretched over it; the pericardial sac contained no fluid. The right auricle was distended to about three times, and the right ventricle, to about twice its usual size. Each was filled with dark fluid blood. The left auricle and ventricle were firm-walled, collapsed and empty. The left ventricular myocardium was firm, its papillary muscle contracted; that of the right ventricle was thin and toneless, its papillary muscle flabby. The valves and endocardium were normal.

The heart weighed 97 Gm. The thickness of left and right ventricle, respectively, without the papillary muscle, was 1.6 and 0.1 cm. The left auricle was 0.3 cm. thick; the right auricle less than 0.1 cm., and very transparent. The diameter of the left ventricle was about 2.8 cm.; the right ventricle, about 7.7 cm.; the left auricle, about 3.4 cm. and of the right auricle about 8.9 cm.

The lungs were moderately emphysematous and diffusely reddened. They could be cut only with some difficulty, the parenchyma, crackling and rebounding under the knife. On section, the cut surface was dry. Bronchioles could be seen only with difficulty and only in very few places.

The liver weighed 1,100 Gm. It showed no gross lobulation, the cut surface being diffusely brown and dulled. The spleen weighed 72 Gm. Its capsule was tense, its consistency soft; on section, the cut surface was mushy, semisolid and of a dull beet-red color in which neither corpuscles nor trabeculae could be distinguished.

Microscopic Examination.—All the alveoli were widely distended and empty, and the alveolar walls were thin and ruptured in places. The bronchiolar epithelium was arranged evenly in deep folds around the entire circumference; the whole layer was separated from the underlying wall by a narrow, clear zone. The bronchiolar lumina were quite narrowed. The arteriolar walls were thickened, their elastic layers markedly folded, their lumina narrow, empty, and in places nearly obliterated where the arteriolar walls were in apposition. An occasional rather large arterial vessel appeared widely dilated and filled with a compact mass of well preserved erythrocytes. Such vessels showed their elastic layers without any folds, and circular throughout. Many other large vessels (without definite elastic layer and presumably venous in character) were irregular in outline; their lumina were distinct and entirely empty.

The lobules of the liver were indistinctly outlined by a few narrow sinusoids containing a few erythrocytes in the extreme periphery of the lobule. In places there appeared a small central vein, quite round, and entirely filled with masses of red cells. Elsewhere throughout the section, no distinct sinusoids were distinguishable, or they appeared as narrow, empty, irregular spaces. The hepatic cells were large, contiguous but nowhere in the form of regular cords, the cells forming a very irregular network. The cellular cytoplasm was coarsely granular, pale acidophilic, and devoid of glycogen. The nuclei were small and deeply and homogeneously basophilic. No changes were noted in the occasional Kupffer cell seen. In the portal spaces, the arterial radicles were narrow, thick-walled, and frequently without discernible lumen, while the venous branches were large, round and filled with erythrocytes.

The spleen showed a distinct congestion of the sinuses and a moderate edema of the corpuscles, most of which contained nests of concentric epithelioid cells which in places were entirely necrotic.

The kidneys, brain cortex and suprarenals showed a pronounced congestion of their capillaries.

Bacteriologic Examination.—The antemortem nasal cultures were negative for Klebs-Loeffler bacilli but postmortem cultures were positive. Antemortem pharyngeal culture was positive for Klebs-Loeffler bacilli.

REVIEW OF LITERATURE

Klotz[3] reported the case of a 2 year old child who did not have a history of asthma, and who had had no injections of foreign protein previously. Intramuscular injection of 1.2 cc. of diphtheria antitoxin produced death in ten minutes. At autopsy, the thymus was found "enlarged."

3. Klotz, O.: Montreal M. J. **36**:615, 1907.

Kortright [4] reported the case of a 16 year old girl who gave no history of asthma or urticaria, and who had had no previous injection of foreign protein. Five minutes after the intramuscular injection of 10 cc. of diphtheria antitoxin, she developed generalized tingling sensation and a sense of a lump in her stomach; she became quite restless, and developed tonic, then clonic, convulsions and opisthotonos. She became cyanotic and died, apparently from respiratory failure; the heart continued to beat for three minutes after respiration had ceased. The entire process from onset of symptoms until death occurred lasted eight minutes. At autopsy, marked congestion of the brain, kidneys and liver was noted.

Gillette [5] had a 52 year old patient with a history of asthma but no previous injection of foreign protein, who was given 2,000 units of diphtheria antitoxin intramuscularly for the asthma. Shortly after the injection, a prickling sensation developed in the chest and neck, and the patient died five minutes after the onset of symptoms, death being preceded by a tonic spasm. Autopsy showed the lungs larger and more voluminous than normal. Status lymphaticus was suggested by the body configuration. The heart was empty and weighted 360 Gm. The spleen was congested; the liver was noted as normal.

Collier and Dreyer [6] recorded the case of an 18 year old girl who had some time (not noted) previously been given a prophylactic dose of diphtheria antitoxin for suspected diphtheria. She had no other history of a previous injection of foreign protein, but had asthma for which an unrecorded amount of diphtheria antitoxin was injected intramuscularly. The patient fell from her chair, dying within a few minutes. Note is made at autopsy that the "lungs and heart were in a condition accounted only for by spasm."

Koch [7] recorded the case of a 6 year old child with diphtheria and without any history of asthma, urticaria or hay-fever, who had been given 1.2 cc. of diphtheria antitoxin intramuscularly. Fourteen days later, 5 cc. of antistreptococcus serum was given intramuscularly and again five hours later 10 cc. of the serum for a complicating scarlatinal infection. Immediately after the latter injection, the child developed facial twitches, its pupils became dilated, its body cyanosed and its thorax immobile; death ensued within two minutes of the injection. Autopsy revealed a fairly pronounced emphysema of the lungs.

4. Kortright, quoted by Halsted, T. H.: Am. J. M. Sc. **130**:863, 1905.

5. Gillette, H. F.: Diphtheria Antitoxin in Bronchial Asthma, J. A. M. A. **50**:40 (Jan. 4) 1908.

6. London Letter, Sudden Death After the Prophylactic Injection of Diphtheria Antitoxin, J. A. M. A. **52**:223 (Jan. 16) 1909.

7. Koch, W.: Berl. klin. Wchnschr. **52**:685, 1915.

Gurd's [8] patient, aged 30, had no history of asthma or previous injection of foreign protein. Five cubic centimeters of tetanus antitoxin given subcutaneously was followed by vomiting in two and one-half hours, after which bloody diarrhea and cyanosis appeared. Death ensued within twenty-four hours. This patient had a history of vomiting and bloody diarrhea five years previously. At autopsy, the lungs were found to be emphysematous and with subpleural "blood collections." Microscopic examination showed alveolar rupture. The bronchioles were contracted and contained red blood cells. The arteries were normal, the veins distended with blood. The heart was noted of normal size and shape, the right ventricle filled with fluid blood and clots and presenting a few subpericardial petechiae. There was a moderate dilatation of the splanchnic vessels, and the spleen, liver and kidneys were congested. The thymus was completely atrophied. The abdominal lymph nodes were larger than normal.

Waugh [9] injected 4,000 units of diphtheria antitoxin intramuscularly into a 17 year old patient with diphtheria who had no history of asthma or urticaria, but who had received diphtheria antitoxin ten years previously. At that time she had become cyanotic and dyspneic, had frothed at the mouth and had been "severely ill." Death with similar symptoms followed within ten minutes after the second injection. The short protocol on the necropsy notes a general venous stasis and pulmonary congestion.

Boughton's patient,[10] aged 29, suffering from horse asthma, had had no previous injection of foreign protein. One minim (0.06 cc.) of horse serum (undiluted?) was injected intravenously for desensitization; death followed within forty-five minutes with typical asthmatic symptoms. Ephedrine gave but slight relief. At autopsy, there was an intense injection of all the vessels of the abdomen, especially those of the stomach, mesentery, gallbladder and appendix. The entire small intestine was reddened, the submucous vessels dilated (microscopic). The parietal peritoneum was injected. The lungs were enormously dilated and emphysematous, with a hemorrhagic area 4 cm. in diameter on the lateral surface of the left lower lobe covered by an organizing gelatinous exudate. Microscopic examination revealed interstitial hemorrhages in this area. The peribronchial and arteriolar muscle was "thick." The heart was firm and of normal size, and showed a few subpericardial petechiae on the posterior surface. Microscopically, small hemorrhages into the myocardium were seen; the small vessels of the

8. Gurd; Fraser and Roberts: Lancet **1**:763, 1920.

9. Waugh, G. H.: Brit. J. Child. Dis. **15**:97, 1918.

10. Boughton, T. H.: Anaphylactic Death in Asthmatics, J. A. M. A. **73**: 1912 (Dec. 27) 1919.

myocardium were apparently thickened. The spleen presented a number of small, reddish-brown bullae 1 mm. in diameter along the anterior border. Microscopically, the kidneys showed interstitial hemorrhages and marked hyperemia; the suprarenals showed hyperemia and contained microscopic hemorrhages. The liver showed edema and "thickened artery walls."

MacCallum [11] reported the case of an 8 year old patient without any previous history of asthma or injection of foreign protein, who within two minutes after receiving 2,000 units of diphtheria antitoxin subcutaneously as a prophylactic measure complained that "it had gone to her stomach." She rapidly became cyanotic, experienced a choking sensation, went into a collapse, and died in five minutes from the time of injection. Autopsy revealed a contracted left ventricle and a flaccid right ventricle filled with dark fluid blood. The mesenteric lymph nodes were caseous. In the stomach was about one-half pint of undigested food (bacon, bread, butter and tea) taken one and one-half hours before the injection.

Dean's patient,[12] aged 22, without any history of asthma or previous injections of foreign protein, had received tetanus antitoxin. Thirteen days later, he received another dose of 500 units of the antitoxin subcutaneously, after which he began to vomit, suddenly became cyanotic, and died within seventy minutes of the injection. Autopsy showed an increased amount of lymphoid tissue in the neck and mediastinum. The liver sinuses (microscopically) were dilated and engorged.

Lamson [2] reported two personal cases. The first patient, aged 17, who had asthma but had had no previous injection of foreign protein, received 750 units of diphtheria antitoxin intramuscularly and died within ten minutes. Autopsy notes recorded only an enlarged thymus.

The second patient, also 17 years of age, without any previous history of asthma or injection of foreign protein, received 500 units of diphtheria antitoxin intramuscularly; he became cyanotic rapidly thereafter, then comatose, developing a marked frothy fluid in the nose and pronounced pulmonary edema ("fluid in lung?"). Death occurred ten minutes from the time of the injection. Autopsy notes stated that the lungs were voluminous and contained a small amount of frothy fluid, and that the thymus was distinctly enlarged.

Mendeloff [13] reported the case of a man who died within a few minutes after the injection of antimeningococcus serum. Necropsy showed

11. MacCallum, A. D.: Brit. M. J. **2**:596, 1919.

12. Dean, H. R.: J. Path. & Bact. **25**:305, 1922.

13. Mendeloff: Fatal Anaphylaxis Following Intravenous Injection of Antimeningococcic Serum, J. A. M. A. **82**:1862 (June 7) 1924.

a purulent meningitis and an enlarged thymus. No reference was made to the state of the heart, lungs or vessels, and the author (personal communication) recalled no notation of the state of these organs.

EXPERIMENTAL WORK

Arthur [14] noted a marked drop in blood pressure to zero in a few minutes in instances of anaphylactic shock in rabbits. The chest, opened immediately post mortem, showed the ventricles in systole, the auricles contracting feebly and infrequently. Similar observations were made by Friedberger [15] and Scott,[16] who also noted an extreme congestion of the portal system.

Caesaris-Demel [17] found increased tonus and decreased amplitude of each heart beat of the isolated heart of a sensitized animal perfused with Locke's solution to which the sensitizing protein had been added. No stoppage of the heart was noted. Auer,[18] by direct observation of the thoracic contents during shock, found that the lungs did not collapse as well as normally in the expiratory phase. The heart was slowed, with the right ventricle more distended and tense than usual. Later, small hemorrhages appeared on the surface of the right ventricle, the heart suddenly beat quite slowly, the right auricle did not contract, and the right ventricle filled remarkably and then stopped beating, death ensuing in thirty minutes after injection of the protein. Later,[19] Auer demonstrated electrocardiographic changes indicative of ventricular damage and heart block.

Airila [20] found the pulmonary arterial pressure rising from 7 to 26 mm. of mercury within thirty seconds after the injection of protein with a coincidental drop in systemic blood pressure, the drop occurring near the peak of the high pulmonic pressure. That this drop apparently is not due to an active abdominal vasodilatation, Shultz [21] suggested, the typical systemic blood pressure drop occurring when the entire abdominal area was clamped off before shock was produced. In cats, Edmunds [22] found a rise in pulmonary venous pressure, a peculiar change similarly observed

14. Arthus, M.: Arch. internat. de physiol. **7**:471, 1908-1909.
15. Friedberger, E.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:581, 1909.
16. Scott, W. M.: J. Path. & Bact. **15**:31, 1911.
17. Caesaris-Demel, A.: Gior. d. r. Accad. di med. di Torino **73**:9, 1910.
18. Auer, J.: J. Exper. Med. **14**:476, 1911.
19. Auer, J., and Robinson, G. C.: J. Exper. Med. **18**:450, 1913.
20. Airila, Y.: Skandin. Arch. f. Physiol. **31**:385, 1914.
21. Shultz, W. H., and Jordan, H. E.: J. Pharmacol. & Exper. Therap. **2**:375, 1910-1911.
22. Edmunds, C. W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **22**:181, 1914.

by Drinker and Bronfenbrenner.[23] Coca [24] found the pulmonary blood bed obstructed in the height of shock.

Manwaring,[25] in heart lung preparations of guinea-pigs, found that the flow of very dilute solutions of antigen was stopped if the guinea-pigs had previously been sensitized to it.

Drinker and Bronfenbrenner,[23] whose report is detailed, found that in rabbits in which shock had been produced the pulmonic blood pressure rose within two minutes after the injection of the shock dose, the pressure either began to fall in twenty minutes or remained up for more than two hours. The high pressure may be lowered temporarily by the administration of nitrites. The systemic blood pressure falls and does not return by the end of the experiment. The minute volume of the lungs is increased by an increased respiratory rate, although the respiratory amplitude is lowered. The right auricle and ventricle dilated progressively, death occurring suddenly as in cases of pulmonary embolism or slowly as the result of an inability to maintain the necessary pressure head.

In the cat, an animal sensitized with difficulty, the pulmonary arterial pressure rise is small and well compensated, and the venous pressure falls slightly with the fall in systemic blood pressure, an occurrence which Weil [26] thought indicated a stoppage of circulation by swollen liver cells. In monkeys, a few of which were experimented with, no changes were noted with animals "sensitized" to the blood of guinea-pigs. The authors expressed doubt as to whether sensitization had actually occurred.

COMMENT

The cases reviewed presented clinical manifestations comparable to anaphylactic shock in experimental animals. The postmortem observations, however, showed no marked constancy. Emphysema was seen in six instances, in two of which bronchiolar contraction [8] and peribronchiolar muscular thickening [10] were noted; in the latter case, arteriolar thickening in the lungs, myocardium and liver likewise were present. In only one case [8] was the emphysema apparently extreme enough to cause rupture of the alveolar walls and the presence of subpleural collections of blood, while in another [10] interstitial hemorrhages were present. One case [11] showed dilatation of the right side of the heart as noted in our case; in one case [6] "spasm" was recorded; in two [27] the postmor-

23. Drinker, and Bronfenbrenner, J.: J. Immunol. **9**:387, 1924.
24. Coca, A. F.: J. Immunol. **4**:219, 1919.
25. Manwaring, W. H.: Intestinal and Hepatic Reactions in Anaphylaxis. J. A. M. A. **77**:849 (Sept.) 1921.
26. Weil, R.: J. Immunol. **2**:525, 1916-1917.
27. Gurd (footnote 8). Boughton (footnote 10).

tem observations were grossly normal, except for a few subpericardial petechiae, and in one [10] microscopic intramyocardial hemorrhages were noted. The liver was congested in four instances;[28] in one instance edema of the parenchyma was noted, the only observation similar to that experimentally noted by Weil.[26] The spleen was congested in three cases,[29] the kidney in three,[30] the brain in one case,[4] the gastro-intestinal tract and peritoneum in one,[10] and the adrenals in one,[10] in which case interstitial adrenal petechiae were present. In one case,[9] general venous stasis and pulmonary congestion without further details were noted; in one,[8] moderate splanchnic dilatation. More inconstant were the autopsy observations referable to the thymus and the lymphatic system. In three cases, enlarged thymus was present, in one 2 year old child [3] and in two 17 year old patients;[13] in the latter, voluminous lungs were also noted at autopsy; in the other cases, no additional observations are recorded. One case report [5] records "status configuration" congested spleen and voluminous lungs. In one case,[6] atrophic thymus and enlarged abdominal lymph nodes were noted in a 30 year old patient; in this case the previous history of bloody diarrhea and vomiting and the presence of enlarged abdominal nodes suggests the possibility of an old intestinal tuberculosis. One patient,[12] 22 years old, showed an increased amount of lymphoid tissue in the neck and mediastinum. In this group no mention is made of hypoplasia of the heart, vessels or other viscera further than to substantiate the diagnosis of status lymphaticus. It does not seem possible to correlate these observations with the death of the patients.

Nor does there seem to be any correlation between the presence of previous anaphylactic symptoms or injection of foreign protein with the presence of thymic or hyperplastic lymphoid tissue. In the group showing such tissue four patients presented no previous history of asthma, urticaria or hay-fever, nor had they had any previous injection of protein, while two patients had such a history. In the group showing no suggestion of status lymphaticus, four patients gave no previous history and three patients presented such data.

These anatomic observations vary considerably and are incompletely described in many instances. The emphysema and general venous stasis and parenchymal congestion are prominent. In several cases, arteriolar thickening was noted. In our case, we demonstrated thickening of the pulmonary arterioles; the elastic membranes were wrinkled markedly so as to suggest the presence of marked spasm. The extreme dilatation of

28. Kortright (footnote 4). Gurd (footnote 8). Dean (footnote 12). Boughton (footnote 10).

29. Gillette (footnote 5). Gurd (footnote 8). Boughton (footnote 10).

30. Kortright (footnote 4). Gurd (footnote 8). Boughton (footnote 10).

the right side of the heart with general congestion and markedly contracted left side of the heart devoid of fluid contents or blood clots seem further to substantiate the belief that the cause of death in anaphylactic shock is failure of the right side of the heart and inability to maintain pressure in the pulmonary system as the result of obstruction of the arteriolar pulmonary blood bed, as indicated by the experimental work cited.

SUMMARY

1. A case of fatal anaphylactic shock after a single injection of diphtheria antitoxin is reported.

2. The pathologic anatomy is described, consisting chiefly of acute pulmonary emphysema, dilatation of the right side of the heart, general venous stasis and visceral congestion; the left side of the heart is contracted and empty. Microscopically, the changes consist chiefly of thickening of the arteriolar wall, especially in the lungs.

3. These anatomic changes are presented as corroborative morphologic evidence to substantiate the experimental work on the pathogenesis of fatal anaphylactic shock reviewed. This consisted chiefly in overfilling of the lungs, which remained distended, a drop in the peripheral blood pressure with a concomitant rise in the pulmonary arterial pressure, a progressive weakening of cardiac contraction and a slowing and final stopping of the heart, with the right auricle and ventricle in diastole and very much dilated.

4. The cases of anaphylactic shock which came to autopsy are reviewed in detail. Doubt is cast on the rôle of the thymus in such cases.

THE INFLUENCE OF A SPECIAL BREAKFAST ON THE BASAL METABOLISM OF PATIENTS WITH A PATHOLOGIC CONDITION *

CHI CHE WANG, PH.D.
AND
JEAN E. HAWKS, M.S.
CHICAGO

Benedict [1] demonstrated that a special breakfast consisting of 200 cc. of coffee free from caffeine, 16 mg. of saccharin, 30 Gm. of medium cream and 25 Gm. of potato chips had little or no effect on the production of basal heat in normal subjects if the test was made one hour or longer after the meal. However, he did not recommend the use of such a meal without further investigation in cases of patients with a pathologic condition. In view of the practical application of such a breakfast to pathologic cases, the present study was conducted.

DuBois,[2] in his study of the metabolism of boys between the ages of 12 and 13, also employed a small breakfast consisting of one egg, one slice of toast with butter and a glass of milk. The test was made four hours after the meal. Higgins [3] used the same breakfast in his study made on a young man, and found that the production of heat returned to basal value in three and one-half hours after the meal. Later DuBois and his associates [4] demonstrated that the production of heat in five adults was 2 per cent above their basal value two hours after the ingestion of a meal consisting of one slice of bread, 8 Gm. of butter, 10 Gm. of sucrose and 60 Gm. of milk. Six hours later, the value was slightly below the fasting level. In the study of the basal metabolism of children, Bauer and Blunt [5] employed a special breakfast with a fuel value varying from 200 to 470 calories, and the protein content from

* Submitted for publication, Dec. 11, 1929.

* From the Nelson Morris Institute for Medical Research of the Michael Reese Hospital, Chicago, aided by the Gusta Morris Rothschild Fund and the S. J. T. Straus Fund.

1. Benedict, C. G., and Benedict, F. G.: A Permissible Breakfast Prior to Basal Metabolism Measurements, Boston M. & S. J. **188**:849 (May) 1923.

2. DuBois, E. F.: Clinical Calorimetry. XII. The Metabolism of Boys 12 and 13 Years Old Compared with the Metabolism at Other Ages, Arch. Int. Med. **17**:887 (June) 1916.

3. Higgins, quoted by DuBois (footnote 2).

4. Soderstrom, G. F.; Barr, D. P., and DuBois, E. F.: Clinical Calorimetry. XXVI. The Effect of a Small Breakfast on Heat Production, Arch. Int. Med. **21**:613 (May) 1918.

5. Bauer, V., and Blunt, K.: Effect of a Small Breakfast on the Energy Metabolism of Children, J. Biol. Chem. **59**:77 (Feb.) 1924.

TABLE 1.—*Variation of Basal Heat Production Measured One Hour Apart*

								Heat Production					
								Fasting					
								First Test		One Hour Later		Difference	
Name	Sex	Age	Height, Cm.	Weight, Kg.	Pulse	Temperature	Predicted Calories per 24 Hours H-B	Calories per 24 Hours	Per Cent Variation from Normal	Calories per 24 Hours	Per Cent Variation from Normal	Calories per 24 Hours	Per Cent	Diagnosis
L. F.	F	55	154	52.4	71	98.1	1,184	1,684	+42.2	1,645	+38.9	— 39	— 2.3	Thyrotoxicosis
S. Wi.	F	38	162	47.0	71	97.2	1,227	1,639	+33.6	1,577	+28.5	— 61	— 3.7	Thyrotoxicosis
H. W.	M	36	161	51.7	92	97.4	1,339	1,728	+29.1	1,775	+32.6	+ 47	+ 2.7	Thyrotoxicosis
E. B.	F	58	143	36.6	75	97.4	998	1,132	+13.4	1,111	+11.3	— 21	— 1.9	Decompensated heart
A. J.	F	43	165	48.0	86	98.2	1,217	1,362	+11.9	1,429	—17.4	+ 67	+ 4.9	Tumor of cecum
S. A.	M	57	170	58.0	65	97.7	1,330	1,486	+11.7	1,594	+19.9	+108	+ 7.3	Decompensated heart
D. W.	F	55	159	71.5	66	98.6	1,376	1,536	+11.6	1,378	+ 0.2	—158	—10.3	Thyrotoxicosis
B. K.	F	29	166	70.8	76	98.6	1,504	1,678	+11.5	1,581	+ 5.1	— 97	— 5.7	Thyrotoxicosis
R. R.	F	75	154	59.6	77	97.7	1,159	1,292	+11.4	1,286	+10.9	— 6	— 0.4	Carcinoma; thyrotoxicosis; diabetes
S. W.	F	45	144	56.5	97	98.2	1,247	1,374	+10.2	1,270	+ 1.8	—104	— 7.6	Peptic ulcer; rheumatism
W. T.	F	28	161	49.6	96	97.8	1,296	1,360	+ 4.9	1,352	+ 4.3	— 8	— 0.6	Thyrotoxicosis
M. H.	M	29	172	65.8	51	97.4	1,636	1,679	+ 2.6	1,697	+ 3.7	+ 18	+ 1.1	Jaundice
J. R.	M	23	160	42.5	99	98.2	1,294	1,312	+ 1.4	1,302	+ 0.6	— 10	— 0.8	Spinal meningitis
M. D.	F	61	148	51.4	71	98.2	1,135	1,149	+ 1.2	1,098	— 3.2	— 51	— 4.4	Cholecystitis
J. M.	M	21	180	69.0	80	99.0	1,774	1,781	+ 0.4	1,861	+ 4.9	+ 80	+ 4.5	Lymphosarcoma
J. H.	F	27	166	60.7	80	98.6	1,417	1,361	— 3.9	1,443	+ 1.8	+ 82	+ 6.0	Normal
S. K.	F	29	156	51.4	90	98.7	1,300	1,237	— 4.8	1,263	— 2.8	+ 26	+ 2.1	Endocarditis
J. C.	F	22	168	57.5	67	98.4	1,413	1,286	— 9.0	1,370	— 3.0	+ 84	+ 6.5	Normal
M. S.	M	20	184	73.1	61	97.4	1,858	1,685	— 9.3	1,768	— 4.9	+ 83	+ 4.9	Normal
D. R.	F	34	163	112.4	66	97.8	1,872	1,635	—12.7	1,622	—13.3	— 13	— 0.8	Obesity and cholecystitis
Average									+ 7.87	.....	+ 7.74	+ 1.35	+ 0.06	

3 to 13.8 Gm. The average consumption of oxygen taken from three and one-half to four hours after the meal was 0.6 per cent above the fasting level.

EXPERIMENTAL WORK

A total of ninety-six experiments were made on a group of three laboratory workers serving as controls and on twenty-two patients of whom twelve were suffering from thyrotoxicosis, three from cardiac disturbances, and the others from diabetes, jaundice, obesity, rheumatic fever, meningitis and cholecystitis. All the precautions for a true basal test were carefully followed, and each patient had had several tests before this investigation was undertaken. A resting period of thirty minutes preceded each test. In the control series, which was conducted on fourteen females and six males, a second test was made one hour after the first, during which interval the patients were allowed to sit up for one-half hour. In addition to the twenty people who served as subjects in the control series, five patients (four males and one female) suffering from thyrotoxicosis were used in the second series. In this series the patients received the special breakfast recommended by Benedict[1] after the basal test, and a second test was made one hour later. The Roth-Benedict[6] respiration apparatus was employed throughout this investigation, and the results were compared with the Harris-Benedict standards.[7]

RESULTS

In the control series the production of heat for the first test ranged from + 42.2 to — 12.7 and the second test from + 38.9 to — 13.3 per cent as compared with the standards. The difference between the two tests varied from + 108 to — 158 calories per twenty-four hours with a maximum variation of 10.3 and a minimum of 0.4 per cent. The average difference of the two tests was 1.35 calories, or 0.08 per cent. In the second series the percentage variation in the production of heat for the first test ranged between + 74.6 and — 14.6, while the corresponding values for the test made one hour after the meal were + 68.3 and — 11.8 per cent as compared with the standards. The difference between the two tests was from + 144 to — 173 calories per twenty-four hours with a maximum difference of 8.9 and a minimum of 0.5 per cent. The average difference of the two tests was 1.75 calories, or 0.53 per cent. In comparing the two series the difference in the production of heat for the two tests made on normal subjects was smaller in the second series than in the control. The average percentage difference of the control series was + 5.8 as compared with + 0.7 of the second series. All but one of the six patients suffering from thyrotoxicosis who served as subjects in both series gave a greater percentage difference

6. Roth, P.: Modifications of Apparatus and Improved Technic Adaptable to the Benedict Type of Respiration Apparatus, Boston M. & S. J. **186**:457, 1922.

7. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Washington, D. C., Carnegie Institution of Washington, 1919, p. 279.

TABLE 2.—*Variation in Basal Metabolism One Hour After a Small Breakfast*

Name	Sex	Age	Height, Cm.	Weight, Kg.	Pulse	Temperature	Predicted Calories per 24 Hours H-B	Heat Production: Fasting: Calories per 24 Hours	Heat Production: Fasting: Per Cent Variation from Normal	Heat Production: 1 Hour After Food: Calories per 24 Hours	Heat Production: 1 Hour After Food: Per Cent Variation from Normal	Heat Production: Difference: Calories per 24 Hours	Heat Production: Difference: Per Cent	Diagnosis
D. M.	M	52	170	57.8	..	....	1,360	2,374	+74.6	2,290	+68.3	— 84	—3.5	Thyrotoxicosis
S. W.	F	38	162	46.9	96	....	1,225	1,972	+61.0	1,849	+50.1	—123	—6.2	Thyrotoxicosis
W. M.	M	33	162	41.7	..	....	1,228	1,974	+60.7	1,933	+57.4	— 41	—2.0	Thyrotoxicosis
S. Wi.	F	38	162	47.2	84	99.1	1,228	1,813	+47.6	1,938	+41.5	— 75	—4.1	Thyrotoxicosis
S. B.	M	40	184	78.4	97	97.8	1,793	2,644	+47.4	2,504	+40.0	—140	—5.3	Thyrotoxicosis
L. F.	F	55	154	52.7	73	98.6	1,187	1,732	+45.9	1,702	+43.4	— 30	—1.7	Thyrotoxicosis
N. W.	M	36	162	50.6	92	97.5	1,329	1,835	+38.1	1,805	+35.8	— 30	—1.6	Thyrotoxicosis
R. R.	F	75	155	59.6	88	....	1,161	1,569	+35.1	1,645	+41.7	+ 76	+4.8	Thyrotoxicosis; carcinoma; diabetes
K. M.	M	50	166	63.7	..	....	1,435	1,933	+34.7	1,760	+22.6	—173	—8.9	Thyrotoxicosis
N. W.	M	36	161	49.8	92	98.4	1,313	1,755	+33.7	1,899	+44.6	+144	+8.3	Thyrotoxicosis
R. R.	F	75	154	59.4	83	97.4	1,158	1,496	+29.2	1,574	+35.9	+ 78	+5.2	Thyrotoxicosis; carcinoma; diabetes
D. W.	F	55	159	72.7	90	98.4	1,386	1,750	+26.3	1,723	+24.3	— 27	—1.5	Thyrotoxicosis
S. A.	M	59	170	57.3	66	97.2	1,320	1,587	+20.2	1,506	+14.1	— 81	—5.1	Decompensated heart
B. K.	F	29	165	71.2	72	98.0	1,506	1,773	+17.7	1,835	+21.8	+ 62	+3.5	Thyrotoxicosis
A. G.	F	40	145	46.4	..	....	1,180	1,352	+14.6	1,374	+16.4	+ 22	+1.6	Thyrotoxicosis
E. B.	F	58	143	37.3	69	98.6	1,006	1,138	+13.1	1,212	+20.5	+ 74	+6.5	Decompensated heart
A. J.	F	43	165	48.5	81	98.4	1,222	1,310	+ 7.2	1,354	+10.8	+ 44	+3.4	Tumor of cecum
J. R.	M	23	160	41.8	110	97.6	1,286	1,348	+ 4.8	1,341	+ 4.3	— 7	—0.5	Spinal meningitis
Sa. W.	F	45	145	56.2	114	98.3	1,250	1,310	+ 4.8	1,377	+10.2	+ 67	+5.1	Rheumatic fever; peptic ulcer
M. H.	M	29	172	66.5	52	97.5	1,646	1,696	+ 3.0	1,793	+ 8.9	+ 97	+5.7	Jaundice
J. M.	M	21	181	70.3	77	98.6	1,797	1,848	+ 2.8	1,936	+ 7.2	+ 88	+4.8	Lymphosarcoma
W. T.	F	28	161	50.0	99	97.7	1,300	1,298	— 0.1	1,306	+ 0.4	+ 8	+0.6	Thyrotoxicosis
M. S.	M	20	184	72.8	63	97.9	1,852	1,834	— 1.0	1,884	+ 1.7	+ 50	+2.7	Normal
M. D.	F	61	148	51.5	72	98.0	1,136	1,116	— 1.7	1,104	— 2.8	— 12	—1.1	Cholecystitis
J. H.	F	27	166	61.3	71	98.2	1,421	1,368	— 3.7	1,335	— 6.1	— 33	—2.4	Normal
J. C.	F	22	168	56.9	65	98.0	1,407	1,246	—11.4	1,269	— 9.8	+ 23	+1.8	Normal
S. K.	F	29	156	51.0	83	98.6	1,296	1,140	—12.0	1,160	—10.5	+ 20	+1.8	Endocarditis
D. R.	F	34	162	111.8	68	97.6	1,865	1,592	—14.6	1,644	—11.8	+ 52	+3.3	Obesity; cholecystitis
Average									+20.6	.....	+20.7	+ 1.75	+0.53	

between the two series than the normal subjects. However, the difference was so slight that it was less than the difference between two tests made on the same patient on different days under identical conditions. Thus, N. W., on whom two experiments in the second series were conducted several days apart, gave the percentage difference of the two tests (one taken before and one after the meal) of — 1.6 and + 8.3, whereas the corresponding value for the experiment in the control series was + 2.7. The difference in the production of heat brought about by the special breakfast on all the other patients was within the range of those already discussed. Thus our results are in agreement with those of Benedict [1] on normal subjects.

Based on the foregoing data, it is concluded that the special breakfast recommended by Benedict [4] may be used with advantage to a patient who has a late appointment for a basal metabolic test. Such a breakfast may have the following advantages: (1) it may minimize the nervousness of the patient, which is usually caused by the prolonged waiting; (2) it may relieve the discomfort caused by hunger; and (3) it will enable laboratories to perform metabolic tests in the afternoon.

SUMMARY

Two series of experiments were conducted on three normal persons and on twenty-three subjects with a pathologic condition, including twelve patients with thyrotoxicosis. The basal metabolism varied from + 74.6 to — 14.6 per cent from the Harris-Benedict standard. In the control series two tests were made one hour apart, while in the second a special breakfast recommended by Benedict was given after the first test, followed by another test an hour later. The average difference of the two tests in the control series was 0.08 per cent while that of the second series was 0.53.

On the basis of our experimental data, we conclude that the special breakfast may be used with advantage to patients who are extremely nervous and who have late appointments for their basal metabolic test.

THE INTERMEDIATE METABOLISM OF FOREIGN SUGARS *

ELLA H. FISHBERG, M.D.
AND
B. T. DOLIN, M.A.
NEW YORK

The recent development of a rapid method for the estimation of foreign sugars in the blood in the presence of dextrose [1] throws new light on the chemical nature of the reducing substances circulating in the blood stream under normal and pathologic conditions. The methods that have previously been used for this determination fall into three classes: (1) physical methods (polariscopy, etc.), (2) chemical methods, dependent on the rate of reaction of the various sugars under fixed conditions, and (3) biologic methods which depend on the selective action of living organisms. The chemical reactions have not been sufficiently specific. It has been very difficult to get the sugar solution pure enough for physical measurements because of the variety and great number of other optically active substances always present in the blood.

The application of yeast fermentation, which theoretically should remove all the dextrose, has resulted in entirely conflicting data. Neuberg [2] attributed these discordant results to reducing and optically active substances formed during the fermentation, even when pure dextrose solutions and pure yeast cultures are used. Folin and Svedberg [3] showed that eight minutes' incubation with yeast completely destroyed the blood dextrose. Somogyi found the reaction almost instantaneous, and that at room temperature a simple substitution of a 10 per cent (moist weight) yeast suspension, for the distilled water for laking and dilution in the Folin-Wu tungstic acid precipitation of the blood proteins, results in the total destruction of the dextrose in the blood, leaving intact other sugars such as xylose, galactose and lactose. This gives a method of estimating the actual content of the nonfermentable sugars in the presence of dextrose, where previously one could estimate only the total sugar. Certain problems in the intermediate metabolism of the foreign sugars become simplified; as, for instance, the extent to which the

* Submitted for publication, Jan. 7, 1930.

* From the Chemical Laboratory of Beth Israel Hospital.

1. Somogyi, M.: J. Biol. Chem. **75**:33, 1927.
2. Neuberg, C.: Biochem. Ztschr. **24**:430, 1910.
3. Folin, F., and Svedberg, A.: J. Biol. Chem. **70**:405, 1926.

foreign sugar tends to take the place of the normal dextrose and the amount of sugar actually liberated by the glycogenic depots in response to the stimulus of the dextrose hypoglycemia engendered by the foreign substance.

The rate of change of concentration (C) in the blood is dependent on four factors: the addition (a), the destruction (δ), the storage (ψ) and the excretion (ϵ).

$$\frac{d\,c}{d\,t} = \phi\,(a, \delta, \psi, \epsilon)$$

a can be known and ϵ can be measured, but lack of knowledge of the interrelationships of δ and ψ makes it impossible to solve the differential equation. It is undoubtedly true that some of the nonassimilable sugar is excreted into the intestine and the bacterial destruction takes place there. In a sugar such as xylose or any of the other pentoses the main channel of excretion is through the kidneys, and a very high portion of it can be accounted for in this fashion. Hence any changes in the permeability of the kidney membrane should be of enormous importance in regulating the amount of pentose in the blood. The results of animal experimentation and also one case of nephritis show this to be true.

The changes in the concentration of galactose in the blood are influenced by more factors, since galactose is more closely akin to dextrose. Here the factor ψ comes into play to a larger extent. Galactose has been reported as able to relieve insulin intoxication,[4] and has a somewhat therapeutic effect in relieving the hypoglycemia following the total extirpation of the liver, as reported by Mann and Magath.[5] Hence it is definitely changed in the liver into glycogen, which is able to respond to the stimulus of hypoglycemia to be converted into dextrose. The liver function tests with ingested galactose are based on the assumption that the healthy liver will dispose of a certain amount of foreign sugar in a definite time. However, it must always be kept in mind that the liver has amazing compensatory functional powers, and the presence of a minimum amount of normal tissue will still maintain normal function when the pathologic anatomic picture gives an appearance of almost total tissue destruction. Hence negative results are by no means conclusive of the absence of liver destruction. We have, however, found that in experimental phosphorus poisoning (when carried out over a period of from six to eight weeks and more) resulting in pathologic lesions similar to those found in man as a result of chronic liver disease, we could get much delayed destruction of the

4. Noble, E. C., and McLeod, J. J.: Am. J. Physiol. **64**:547, 1923.

5. Mann, F., and Magath, T.: Studies on Physiology of Liver: Effect of Administration of Glucose in the Condition Following Total Extirpation of Liver, Arch. Int. Med. **30**:171 (Aug.) 1922.

galactose administered. The kidney also disposes of some of the excess galactose, and in cases of chronic nephritis in man we could also get delayed disappearance of the galactose from the blood, as well as in experimental uranium nephritis in rabbits.

METHOD OF SUGAR DETERMINATION

A weighed amount of Fleischman's yeast was suspended in ten parts of water and repeatedly centrifugated till the supernatant liquid was clear and the last washing caused no reduction of copper solutions. The yeast was suspended in ten parts of water and kept in the icebox, being centrifugated every morning and the supernatant fluid being replaced by clear water.

TABLE 1.—*Distribution of Fermentable and Nonfermentable Reducing Substances in Normal Patients*

Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Dextrose, Mg. per 100 Cc.
103	24	79
74	31	43
113	32	81
73	34	39
84	22	62
88	29	59
74	31	43
89	26	63
112	24	88
107	25	82
92	27	65
111	29	82
124	29	96
101	24	77
86	28	58

Two cubic centimeters of blood was dropped into 2.3 cc. of water and 1 cc. of 33 per cent solution added and shaken for a minute. Then 0.5 cc. of tungstic acid (made by 0.5 cc. of two-thirds normal sulphuric and 0.5 cc. of 10 per cent sodium tungstate solution) was added and centrifugated. Of the clear fluid 2 cc. was used and the reducing substance determined by the Hagedorn-Jensen[6] method. It is, of course, understood that the usual Folin method may be used, and in this case one part of blood with seven parts of 10 per cent yeast suspension, and then one part each of the sulphuric acid and sodium tungstate were added, and the filtrate used exactly as the usual Folin-Wu filtrate.

A series of determinations was done on cases selected at random from the wards, but not showing any disturbance in metabolism, as for example corneal ulcer, appendicitis, Colle's fracture, etc.

The average nonfermentable fraction for normal reducing substance of the blood is about 28 mg. per hundred cubic centimeters, which is

6. Hagedorn, H. C., and Jensen, B. N.: Biochem. Ztschr. **135**:46, 1923.

in agreement with the observations of Somogyi. In a second series of cases in which all patients were suffering from disturbances of metabolism, the ratio between the fermentable and the nonfermentable reducing substance of the blood was determined.

In table 2 it is shown, in agreement with the results of Somogyi, that in uremic patients with a high nonprotein nitrogen content of the blood, there is a distinct rise in the nonfermentable reducing substances. However, in the case of diabetic patients we found, in contrast with the figures given by Somogyi, a distinct rise in the nonfermentable

TABLE 2.—*Distribution of Fermentable and Nonfermentable Reducing Substances in Metabolic Disorders*

Disease	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Dextrose, Mg. per 100 Cc.	N. P. N.
Diabetes mellitus	212	84	128	...
Diabetes mellitus	208	38	170	...
Diabetes mellitus	194	45	149	...
Diabetes mellitus	495	90	405	...
Diabetes mellitus	201	49	152	...
Diabetes treated with insulin	109	40	169	...
Diabetes treated with insulin	121	34	87	...
Hypoglycemia (overdosage of insulin)	41	24	17	...
Hypoglycemia (overdosage of insulin)	34	23	11	...
Hypertension	184	41	143	...
Hypertension	176	39	137	...
Hypertension	164	38	126	...
Uremia	154	64	90	161
Uremia	182	51	131	131
Uremia	151	60	91	394

fraction, and we have found figures as high as 90 mg. per hundred cubic centimeters, in agreement with the results of Lund and Wolf.[7] In cases of hypertension showing rather high figures of the total blood sugar, we found distinctly higher residual reducing values. In two cases of hypoglycemic shock, we found normal values of the nonfermentable reducing substance in agreement with the results found by van Slyke [8] in the experimental hypoglycemia of rabbits.

Another series of cases that yielded high nonfermentable reducing substances in the blood was that of women in the late stages of pregnancy. These figures were especially high, reaching between 70 and 90 mg. per hundred cubic centimeters just before and during labor.

7. Lund, G. S., and Wolf, C.: Biochem. J. **20**:263, 1926.

8. Hiller, A.; Linder, G. C., and Van Slyke, D. D. J. Biol. Chem. **64**:625, 1925.

FATE OF FORGEIN SUGARS INJECTED INTO THE BLOOD STREAM OF RABBITS

Varying amounts of sugar were injected into the marginal veins of rabbits and the blood taken at intervals by simple incision of the vein in the opposite ear.

It has been found by one of us [9] that the rate of disappearance of the sugar is proportional to the concentration of the sugar itself which is decreasing.

$$\frac{dc}{dt} = -KC$$

Separating the variables and integrating, we have

$$C = Ae^{-Kt}$$

where K is a constant dependent on the unit of time used, and A should be roughly dependent on the amount injected into the blood and the particular method used for the estimation of the sugar. Using any two values of C, we can eliminate A and get a numerical value for K which was found to be 1×10^{-1}. Using this value, we can solve for A. It can be seen from tables 3 and 4 that the value of A is constant with the limits of biologic accuracy. The constancy of A is alike proof of the constancy of K and the correctness of the form of the equation used.

It is at once apparent that the equation $C = A_0^{-Kt}$ is that governing the velocity of a monomolecular chemical reaction. It is thus possible to determine the concentration of the nonfermentable reducing substance at any time in the blood when its concentration at any definite time is known, since the logarithm of the concentration of the foreign sugar at any time is proportional to the time after injection.

Ten milligrams of uranium acetate was injected into a rabbit, and the morning after, the same rabbit was given 2.5 Gm. of xylose injected into the marginal vein. The excretion of the nonfermentable sugar was much delayed through the damage to the kidney tubules. At the end of five hours, the nonfermentable fraction of the blood-reducing substance was still 101 mg. per hundred cubic centimeters. Another rabbit was given subcutaneously into the skin of the abdomen 1 Gm. of phlorizin in two divided doses. On the following day, the animal was excreting 3.4 per cent of sugar in the urine; 2.5 Gm. of xylose was then injected into the ear of this rabbit, and blood taken at intervals and examined for sugar. The nonfermentable reducing substance disappeared from the blood at a much quicker rate than normally, owing to the increased permeability of the kidney membrane caused by the phlorizin (tables 3, 4 and 5 and chart 1). The results are essentially

9. Fishberg, E. H.: J. Biol. Chem. **86**:665, 1930.

TABLE 3.—*Results of Injection of Xylose into the Marginal Vein of Rabbits*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	e^{-kt}	A
Before	114	30	84	.....	...
10	308	233	75	0.905	258
50	267	143	124	0.607	234
85	222	100	122	0.427	234
115	216	79	137	0.317	249
165	174	48	126	0.192	250
220	134	22	112	.....	...
	Injection of 2.5 Gm. of Xylose into Rabbits with Nephritis Caused Uranium				
Before	124	31	93	.....	...
10	315	241	74	.....	...
30	268	175	93	.....	...
60	254	160	84	.....	...
180	221	150	61	.....	...
300	200	159	41	.....	...
480	174	101	73	.....	...
	Injection of 2.5 Gm. of Xylose into a Rabbit with Phlorizin Diabetes				
Before	129	27	102	.....	...
20	439	304	135	.....	...
45	373	194	179	.....	...
70	211	88	123	.....	...
110	185	57	128	.....	...
140	169	24	145	.....	...
170	112	34	78	.....	...

TABLE 4.—*Results of Injection of 5 Gm. of Galactose into a Rabbit*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	e^{-kt}	A
Before	121	32	89	.....	...
5	440	323	117	0.951	339
30	343	230	113	0.741	312
60	331	170	164	0.549	310
90	251	124	127	0.407	307
120	190	96	94	0.301	314
180	181	52	129	0.165	317
225	162	34	128	0.105	338

TABLE 5.—*Results of Injection of 3 Gm. of Galactose into a Rabbit*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	e^{-kt}	A
Before	120	28.5	91.5	.....	....
12	320	248.0	72.0	0.980	253
15	320	189.0	131.0	0.861	223
35	242	160.0	82.0	0.705	228
65	210	112.0	98.0	0.522	218
95	191	86.5	115.5	0.387	222
140	191	54.5	136.5	0.247	221

similar to those obtained by Corley.[10] We also tried the effect of a dose of chloroform (1 cc. administered the evening before), but could find no indication of a changed rate of excretion of nonfermentable reducing substance in the blood. A negative result in this case cannot be interpreted as proof that the intermediate metabolism of xylose is independent of the liver function, because it is well known that even in cases of extreme anatomic damage to the liver, the liver possesses such great compensatory powers that the loss of function is not noticeable.

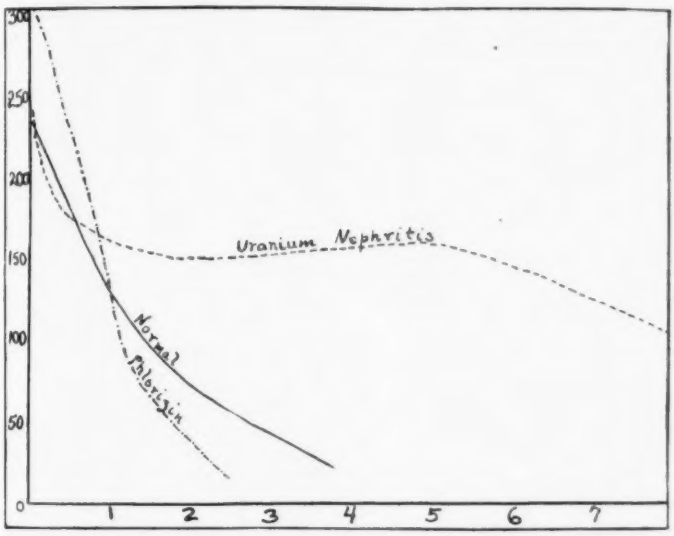

Chart 1.—The effect of an injection of 3 Gm. of xylose into the marginal vein of a rabbit.

A patient having acute nephritis was given 30 Gm. of xylose by mouth. After four hours the reducing, nonfermented fraction of the blood was still above normal. From what is at present known of its intermediate metabolism, xylose should be ideal for a kidney permeability test. However, its present cost makes this difficult.

Three grams of galactose was injected into rabbits and the fermentable and nonfermentable reducing substance measured at intervals thereafter. Five grams of galactose was then injected into another rabbit. It can be seen from tables 4 and 5 that A remains constant and is proportional to the amount injected. Rabbits that had been

10. Corley, R. C.: J. Biol. Chem. **70**:521, 1926.

treated with 10 mg. of uranium acetate were given injections of the same amount of galactose. We noticed a slight delay in the excretion of the galactose as the reducible nonfermenting fraction of the sugar remained for over five hours at a high level. Corley [11] attempted to see if there was any delay in the process of excreting the nonfermentable fraction after one dose of phosphorus. He found that this had no effect, and we were able to confirm his results. However, in those rabbits which had been given phosphorus for six weeks previously, two drops a day, we found a distinct delay in the utilization of the

TABLE 6.—*Results of Injection of 3 Gm. of Galactose into a Rabbit Suffering from Phosphorus Poisoning*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.
Before	118	27	91
2	308	294	114
30	274	231	43
60	231	173	58
90	210	123	87
120	184	114	70
180	201	110	91
360	215	101	114

TABLE 7.—*Results in a Human Being of 60 Gm. of Galactose by Mouth*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.
Before	80	28	52
45	154	133	21
90	250	148	102
135	125	63	62

galactose, the blood showing, after six hours, a residual reduction of 115 mg. per hundred cubic centimeters (table 6).

Sixty grams of galactose ingested by a normal man results in a rise of the total blood sugar to about 250 mg. per hundred cubic centimeters within one and a half hours, and then a sharp fall, so that in two and a half hours, the blood again contains only its normal sugar content (table 7; chart 2). The nonfermentable fraction of the blood rises to a maximum more quickly, reaching there in approximately three quarters of an hour, and stays at that point, giving the typical plateau curve, to one and a half hours, and falling also to reach its

11. Corley, R. C.: J. Biol. Chem. **74**:1, 1927.

normal value within two and a half hours. The fermentable fraction of the blood falls from its normal value at first, probably owing to the flooding of the blood with galactose causing a smaller mobilization of dextrose from the liver. The fermentable fraction reaches its minimum at the time the nonfermentable fraction reaches its maximum. There then comes a sharp rise in the fermentable fraction due to the stimulus of the dextrose hypoglycemia, which reaches its maximum in about one and three quarter hours, and then falls to reach its normal value within two and a half hours.

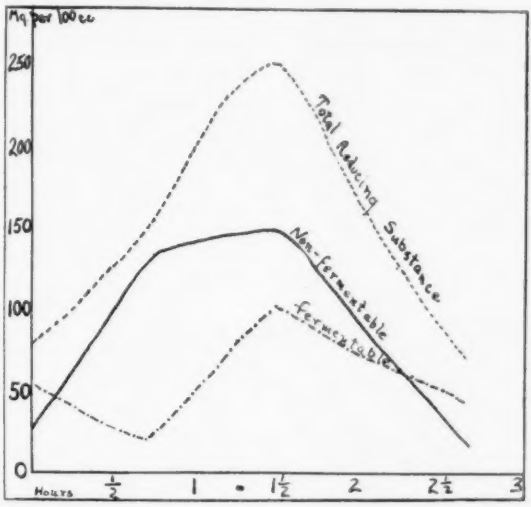

Chart 2.—The effect of the galactose tolerance test in a normal man.

On the ingestion of 60 Gm. of galactose by a patient with diabetes (table 8; chart 3), the total blood sugar rises to a much higher level than that in a normal person, reaching 450 mg. per hundred cubic centimeters. It also reaches this level more slowly. It falls more slowly to its value before the ingestion of the galactose, only reaching the approximate value after four hours. The nonfermentable reducing substance reaches its maximum at the same time as the normal, but tends to stay there, not falling within four hours. In our experiments, the reducing fermentable fraction fell at first and then rose to reach a very sharp maximum in two hours, which, however, was more than

TABLE 8.—*Results in a Diabetic Man of 60 Gm. of Galactose by Mouth*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.
Before	183	112	71
30	192	105	87
90	259	76	183
120	400	230	170
180	242	75	167

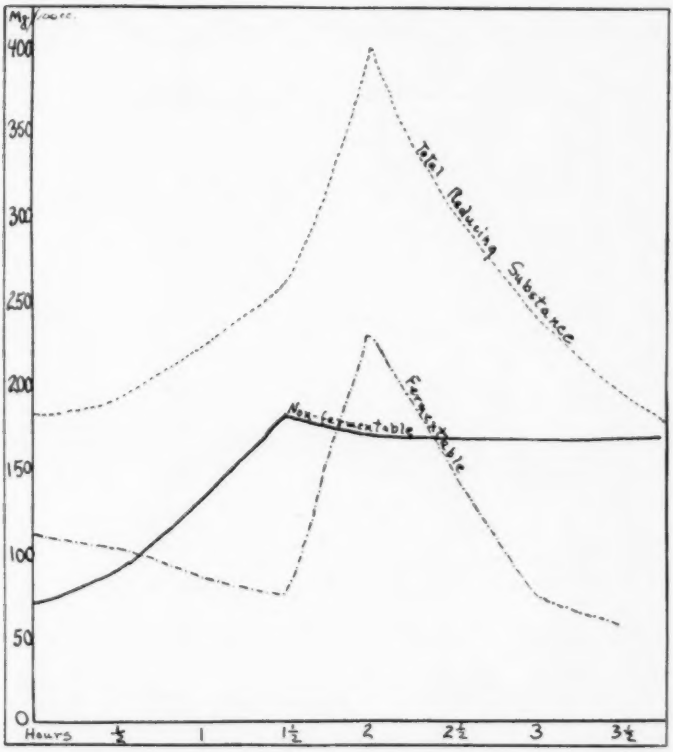

Chart 3.—The effect of an injection of 60 Gm. of galactose into a patient with diabetes.

twice as high as that reached in the normal person. It took three hours for the fermentable sugar to reach its previous value.

Hamman and Hirschmann [12] expressed the view that certain forms of nephritis may affect carbohydrate metabolism. Sixty grams of

12. Hamman, L., and Hirschmann, I. : Blood Sugar, Arch. Int. Med. **20**:761 (Nov.) 1917.

galactose was given by mouth to a patient with nephritis and hypertension, and a delay in the utilization or excretion was found because it took four hours for the reducing nonfermentable substance of the blood to come down to its level of 85 mg. per hundred cubic centimeters. Whether this retention is to be ascribed primarily to the nonpermeability of the kidney membrane or the changed condition of the blood vessels cannot be decided (chart 4).

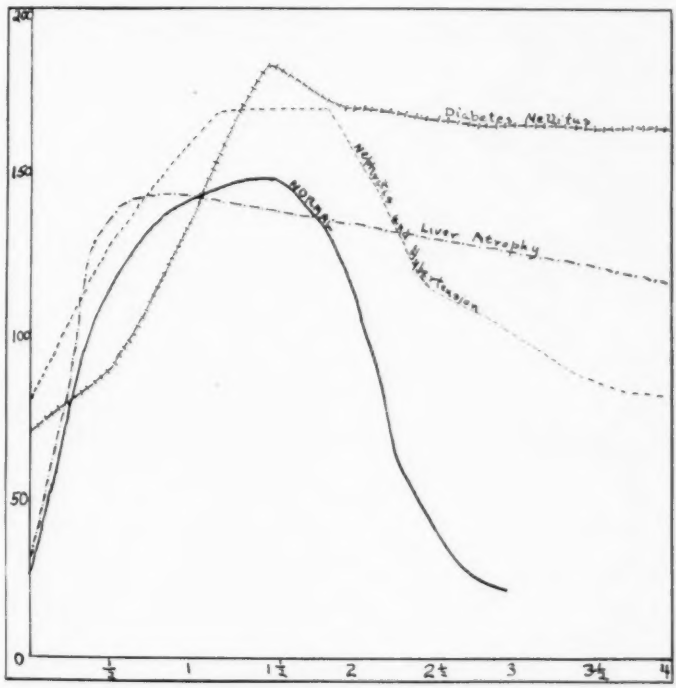

Chart 4.—The ingestion of 60 Gm. of galactose (nonfermentable reducing substance).

SUMMARY

A method is given for the separate determination of xylose and galactose in the presence of dextrose in 0.2 cc. of blood.

The reducing nonfermentable fraction of the blood is remarkably constant in normal human beings, amounting to about 28 ± 5 mg. per hundred cubic centimeters, while in uremia, diabetes, nephritis and lactation this is increased.

Galactose and xylose introduced directly into the blood stream of rabbits disappears at a rate proportional to the actual concentration of the sugar in the blood in accordance with the law governing the velocity of a monomolecular equation. It is thus possible to calculate the nonfermentable reducing substance in the blood at any time, since the logarithm of the concentration of the sugar at any moment is proportional to the time after injection.

Xylose disappears much more slowly from the blood stream of rabbits suffering from uranium nephritis and more quickly from rabbits made diabetic by phlorizin.

Galactose disappears more slowly from the blood stream of rabbits suffering from uranium nephritis and from the blood of those gradually poisoned by phosphorus.

In human beings, galactose disappears more slowly from the blood of patients with nephritis and diabetes.

EPIGASTRIC PULSATION

CLASSIFICATION IN REGARD TO THE FORM OF THE EPIGASTRIOGRAM *

NOBUTATSU FUKUI, M.D.
TOKIO, JAPAN

In a former report, I gave only an outline [1] of my investigation on the epigastric pulsation and its clinical application in the diagnosis of arrhythmia cordis.[2] Later I explained in detail [3] some new problems of epigastric pulsation, in which the epigastric pulsation was investigated as a physical phenomenon from a statistical point of view as well as in relation to the orthodiagram of the heart. In this paper, I shall give the results of the latter report [3] first and then a new classification of the forms of epigastriograms.

STATISTICAL AND ORTHODIAGRAPHIC STUDIES

For the statistical research, the epigastric pulsation is classified into five types, *A*, *B*, *C*, *D* and *E*, as shown in the accompanying table.

Classification of Epigastric Pulsation

			In Ordinary Respiration	In Deep Inspiration
Persons with pulsation (P.)	With marked pulsation = marked P.	A	Marked	Marked
	With moderate pulsation = moderate P.	B	Moderate	Marked
	With slight pulsation = slight P.	C	Slight	Moderate
Persons with nonpulsation (N. P.)	With relative nonpulsation = relative N. P.	D	Missing	Slight
	With absolute nonpulsation = absolute (N. P.)	E	Missing	Missing

Examination of 2,000 healthy men, from 12 to 60 years old, showed that all types of pulsation in those under 20 years of age remain almost constant. Relative nonpulsation (*D*) occurred in 60 per cent; slight pulsation (*C*) in from 20 to 30 per cent; moderate pulsation (*B*) and

* Submitted for publication, Dec. 11, 1929.

* From the Kaigun Medical College, Tsukiji, Tokyo.

1. Fukui, N.: On the Epigastric Pulsation, Acta scholae med. univ. imp. Kioto **7**:41, 1924.

2. Fukui, N.: Epigastric Pulsation; the Diagnosis of the Arrhythmia Cordis Through the Epigastriogram, Arch. Int. Med. **38**:360 (Sept.) 1926.

3. Fukui, N.: Ueber die epigastriche Pulsation, Wien. Arch. f. inn. Med. **15**:349, 1929.

absolute nonpulsation (*E*) in approximately from 5 to 10 per cent; marked pulsation (*A*) was almost missing at this age. In persons over the age of 40 the moderate pulsation (*B*) was present in more than 30 per cent and relative nonpulsation (*D*) in less than 20 per cent. The number of persons with manifest pulsation (*A*) showed a sudden increase. This change begins at the age of 25 to 30 years, and the age of transition from nonpulsation to pulsation should be about 30. Absolute nonpulsation (*E*) was less than 10 per cent in all persons of all ages examined.

The relation between the epigastric pulsation and the proportion between height and chest contour was investigated from the statistical point of view, and it was found that in persons throughout the whole range of ages examined the proportion is always bigger in persons with nonpulsation (N.P.) than in those with pulsation (P).

For details of the investigation of the relation between epigastric pulsation and the orthodiagram of the heart some technical terms have been applied. For instance, the figure indicating the relation between the heart and the subcostal angle is called scrobocardiac figure; the area of the heart included in the subcostal angle is called the grave area; the percentage of the grave area to the entire area of the heart is called area percentage, the distance between the apex of the subcostal angle and the middle of a line formed by the lower border of the heart and subcostal angle is called ptosis distance.

These factors can be measured in two ways, not only in regard to the pulsation (persons with pulsation [P.] and those with nonpulsation [N.P.]), but also in regard to the age (persons over 30 years and those under this age). In these four groups, orthodiagraphic measurement of the heart was made, i. e., breadth, length, inclination, heart area, grave area, area percentage, breadth of radix aortae and ptosis distance and many other factors were measured. The intensity of the epigastric pulsation is related more closely to the area percentage than to the grave area. It is also very interesting to note that the breadth of the aortic root is approximately the same as the ptosis distance, and the epigastric pulsation is related to these two factors; i. e., if the breadth of the aorta is longer than the ptosis distance, the pulsation is weak or missing, and if the latter is longer than the former, the pulsation is stronger.

In the examination of 2,000 healthy men, I found some with asymmetry of the processus xyphoideus. The process deviates to the right side, so that the space between the left costal bow and the process becomes enlarged. In these cases, the ptosis distance is long, the grave area is large, and the epigastric pulsation is intensive (fig. 1).

The registration of the epigastric pulsation is very easy. Just like the venous pulse, it is registered by applying the funnel over the

pulsating area or recorded by Frans' light reflex. The epigastric pulsation is related to respiration, being strong at inspiration and feeble at expiration, this action being opposite to that of the apex beat. By applying this effect of the respiration, the intensity of the pulsation is sometimes controlled in recording it when it is too strong or too weak. In addition to the respiration, the position of the body and the contour of the epigastric region interfere with the epigastriogram.

Analysis of the epigastriogram shows the following components: first, the *a* wave rises, appearing simultaneously with the auricular

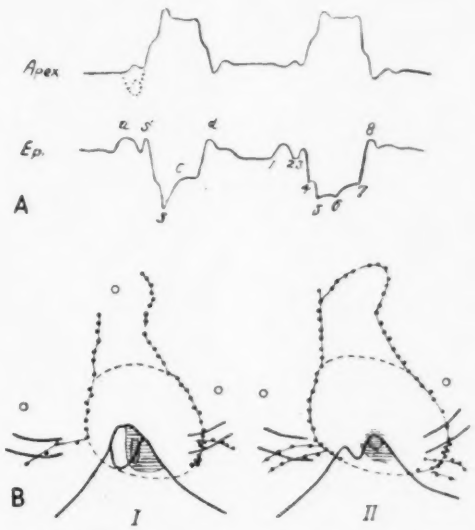

Fig. 1.—In *A*, a typical form of the epigastriogram (Fukui) is compared with that of the apex beat (Wenckbach). The form consists of many components as follows: *1-2*, auricular systole (*a* wave); *2-3*, intersystole; *3-4*, intersystole; *4*, opening of the semilunar valves; *5*, pulsation of the abdominal aorta (*c* wave); *6*, *c* wave, which appears seldom in dissociated wave; *7*, the end of the systole; *7-8*, the beginning of the diastole (*d* wave). *B* shows scrobocardiac figures, in which the processus xyphoideus deviates to the right, and the center of the pulsation lies in the wide space between the left costal bow and the process.

contraction; second, the *s* wave, owing to the muscular shock at the beginning of the ventricular systole, rises sharply and then falls to the *s* valley; third, the *c* wave appears, owing to the pulsation of the abdominal aorta.

The epigastriogram, which consists of the *a*, *s*, *d* and *c* waves, can also be applied to the diagnosis of arhythmia cordis in the same manner as the jugular venous pulse. This is not only very convenient, espe-

Fig. 2.—Epigastriograms with high *s* waves. In *A* and *B*, epigastriograms recorded at inspiration of healthy men, the s wave is relatively high but cannot yet be called the partially positive form. *C* and *D* are epigastriograms of young men of asthenic constitution. This form, in which the plateau from the *d* wave to the *s* wave rises high, is often registered by the asthenic person. *E*, registered at the deep inspiration of athletic young men, is called the partially positive form, in which the *s* wave is highest. *F* and *G*, registered in a case of mitral failure with intensive hypertrophy and dilatation of the left and of the right sides of the heart, show here almost the same figure with the apex beat, for the *s* wave changes into a wide plateau during

cially in cases in which the jugular venous pulse is difficult to register, but also very advantageous on account of the *s* wave, which is missing in the venous pulse.

FORMS OF THE EPIGASTRIOGRAMS

In the former report epigastriograms were classified into various types; for instance, those typical for the asthenic constitution, for pulmonary emphysema, for beriberi, for aortic insufficiency, etc. It must be confessed that this kind of classification is not entirely accurate, and the application of these types of epigastriograms in the diagnosis of the diseases themselves is still less practicable.

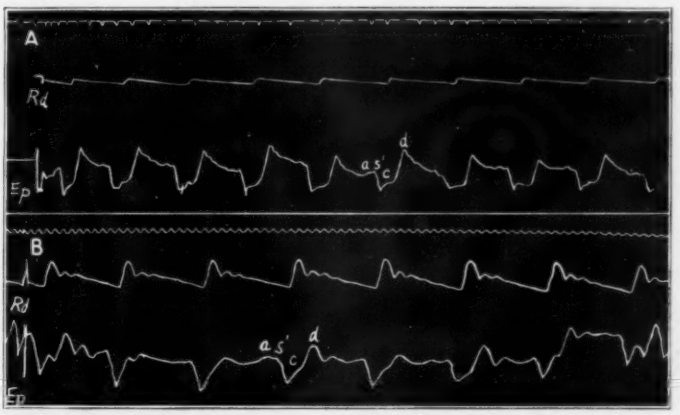

Fig. 3.—Epigastriograms with high *d* waves. In *A*, registered in old men and *B* in old men with bronchial asthma, the *d* wave is highest and the *a* wave also shows manifest elevation.

In this paper the epigastriograms will be classified chiefly in regard to the characteristic of each wave itself, and the epigastriograms will be divided into different types, for instance, an epigastriogram with a high *a* wave, a high *d* wave, a high *s* wave or a high *c* wave. These will be discussed, and some figures will be presented for each group, with explanations.

Epigastriogram With a High S Wave.—The *s* wave is caused by the muscle shock at the beginning of the ventricular systole, and the later greater part of the systole forms the wide *s* valley, in which the pulsation of the abdominal aorta appears. The direction of the movement of the left side of the heart in the ventricular systole is just the opposite of that of the right side of the heart; i. e., the *s* wave is formed by the movement of the left side of the heart and by the abrupt muscle shock

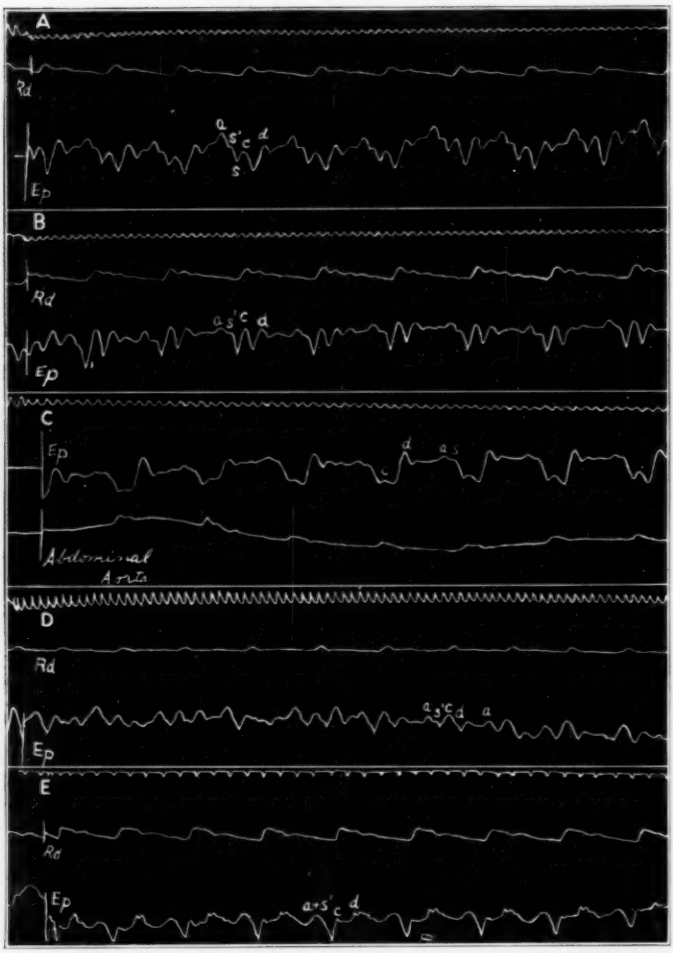

Fig. 4.—Epigastriograms with high *a* waves. *A* and *B* were registered in asthenic young men and *C* in old men with pulmonary emphysema. All these persons have no definite diseases and yet have such a manifest epigastric pulsation, in which the *a* wave rises sharply. *D* and *E*, recorded in cases of beriberi, show a very high *a* wave, which is characteristic for that condition, in addition to other waves, which also rise sharply. The marked elevation of the *a* waves in beriberi is due to the hypertrophy and dilatation of the right side of the heart, which occupies the grave area.

in the beginning of the ventricular systole, while the *s* valley mainly represents the direction of the movement of the right side of the heart.

The sharp rise of the *s* wave means that the movement of the left side of the heart is brought to the epigastrium more easily. The *s* wave rises sharply in the inspiratory phase of the breathing of the normal person, because at inspiration the heart takes the position of the drop heart and the apex of the heart approaches the pulsating heart

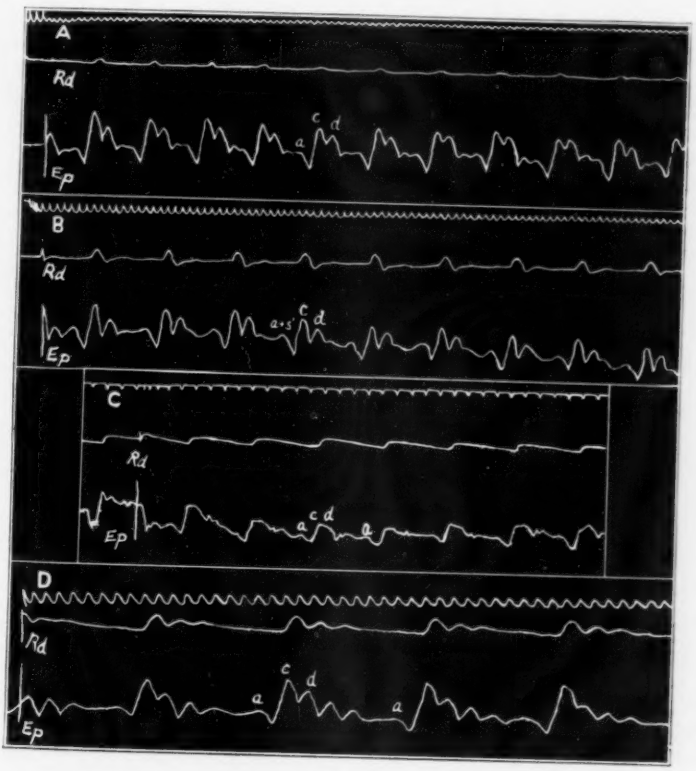

Fig. 5.—Epigastriograms with high *c* waves. *A* and *B*, recorded in patients with fever and *C* and *D* in cases of aortic insufficiency, show high peaks of the *c* wave; *C* and *D* especially are characteristic of aortic insufficiency and have a diagnostic value.

grave. Thus the movement of the apex part and of the anterior left side of the heart, which both represent the movement of the left side of the heart, is led more easily to the scorbiculum cordis. The abrupt change in the direction of the movement of the left side of the heart,

due to the muscle shock, appears in the epigastriogram as a high *s* wave. The inspiratory rise of the *s* wave is apt to occur in the epigastriogram of healthy young persons with hypertrophy of the left side of the heart, especially in the athletic heart. This is due to the same factor as the positive epigastriogram, described later; for the epigastriogram with a high *s* wave is called the partially positive type. It is also interesting to note that a high *s* wave is sometimes obtained in cases of young asthenic persons with drop heart. The high *s* wave is due to the same condition as in the inspiratory phase of breathing. Naturally, this type of epigastriogram is obtained in many other heart diseases in which there is hypertrophy of the left ventricle.

The positive form is the casting figure of the normal epigastriogram, for in the ventricular systole the *s* wave goes into the positive wave instead of falling into the *s* valley, and the *d* wave forms a negative wave. The *c* wave is involved in the systolic swelling and is undetectable, while the *a* wave as a rule appears more distinctly than in the cardiogram for the apex beat. There are, of course, many transitional forms between the positive and the partially positive form; generally speaking, these are due to the same thing, but the positive form is more marked and therefore does not appear so frequently as the partially positive form. The positive form of the epigastriogram is seen in cases of heart disease with greatly hypertrophied and dilated left ventricles, while in normal healthy persons such an epigastriogram is rarely seen. It is interesting to note that the positive form is often seen in cases of decompensation due to mitral failure. But the positive venous pulse, which is characteristic for the arrhythmia perpetua, is due to a totally different cause than that of the positive epigastriogram.

Epigastriogram With a High D Wave.—The *d* wave is formed by the sudden change of the beating of the ventricle, especially of the right, due to the slackness of the heart muscle at the beginning of the ventricular diastole.

The marked rise of this wave has less meaning than that of the other waves. The rise is occasionally seen in the epigastriogram in cases of emphysema and therefore often in the epigastriograms of aged persons. The probable reason for this is the large grave area due to the cardioptosis in emphysema.

Epigastriogram With a High A Wave.—Two factors are given as an explanation of the *a* wave: First, the contraction of the right auricle has an effect on the epigastrium, as shown in the appearance of the *a* wave, just as the contraction of the left auricle has an effect on the *a* wave as shown in the esophagocardiogram, because a small part of the right auricle often lies in the grave area or at least close to it. Second, a sudden change of the volume of the right ventricle due to the

sudden inflow of blood at the contraction of the right auricle is possibly another cause of the *a* wave.

The high peak of *a* wave of the epigastriogram occurs either in cases in which an increased contraction of the right auricle is called for (in many heart diseases, especially typical of the heart in beriberi), or in healthy persons who have a long ptosis distance and a large area percentage, without abnormalities either in the contraction of the right auricle or in the circulation of the lungs. The manifest rise of *a* wave is so typical in beriberi that it often aids in the diagnosis of this condition. This is very interesting in Japan, but the details will be omitted as they have been related in former reports.[4]

Epigastriogram With a High C Wave.—The pulsation of the abdominal aorta not only is an important component of the epigastriogram, but in certain diseases is the determining factor. The *c* wave appears in the *s* valley, a little later than the radial and a little earlier than the carotid pulse, or just between the two pulses. It always serves for the orientation of the epigastriogram. A sharp rise in this wave occurs first in the pulsus celeris, especially in cases of aortic insufficiency, in which the *c* wave is quite typical and has a diagnostic value.

Another noteworthy factor in the high *c* wave is the thin abdominal wall. The aortic pulsation is more easily transmitted, and thus in the case of exophthalmic goiter with emaciation or in an emaciated hyperemic patient, the epigastric pulsation consists almost entirely of the aortic pulsation, which is seen all over the abdominal wall.

Summary of Results.—The epigastriogram is here classified according to its form, for instance, the epigastriogram with a high *s* wave, with a high *d* wave, with a high *a* wave and with a high *c* wave.

The epigastriogram with a high *s* wave changes to the partially positive and the positive form. In healthy persons and especially in persons with athletic hearts the *s* wave rises sharply on inspiration. The positive form is found mainly in heart diseases accompanied by hypertrophy and dilatation of the left side of the heart. The epigastriogram with a high *d* wave has less meaning, often being obtained in the epigastric pulsation of pulmonary emphysema. The epigastriogram with a high *a* wave is recorded not only in cardiac diseases with dilatation of the right side of the heart, but also quite often for healthy persons with a large grave area and ptosis distance. The great rise of the *a* wave is characteristic in beriberi and often serves in the diagnosis of this condition. The epigastriogram with a high *c* wave is obtained in cases of marked celerity in the pulsation of the abdominal aorta, for instance, in patients with fever or with aortic insufficiency; in the latter condition it is typical and has often a diagnostic value.

4. Shimazono, J.: Beriberi, in Stepp and Görgy: Avitaminose und verwendte Krankheit Znstände, Berlin, Julius Springer, 1927, p. 539. Fukui (footnote 3).

GASTRIC SEQUELAE OF CORROSIVE POISONING *

WILLIAM S. BOIKAN, M.D.
AND
HARRY A. SINGER, M.D.
CHICAGO

The immediate effects of corrosive poisoning are well known by the general profession and are fully treated in books on toxicology. The remote results of corrosive ingestion with regard to the esophagus are likewise well understood and extensively dealt with in both periodicals and texts. Concerning gastric sequelae of corrosive poisoning, however, little has been written, especially in the English language. A careful search through the medical indexes for the past fifteen years published in this country or Great Britain yielded few references to late gastric lesions following corrosive poisoning. Halstead [1] told briefly of a midgastric stenosis with obliteration of the pyloric canal following the ingestion of sulphuric acid. Vinson and Hartman [2] discussed a case in which esophageal stenosis effectively treated by dilatation was followed within six months by pyloric stenosis which led to death. Vinson and Harrington [3] reported a case of cicatricial obstruction of the stomach following poisoning with formaldehyde and referred to only one other case of corrosive constriction of the stomach, that of Vinson and Hartman.[2]

From the paucity of reports in American and British medical journals one is led to infer that late structural changes in the stomach following corrosive poisoning are of rare occurrence. The facts, however, do not substantiate this inference. A not inconsiderable number of cases is reported from the continent in countries in which the incidence of corrosive ingestion is no higher than in ours. Furthermore, within less than a year and a half we have encountered at the Cook County Hospital five instances of late gastric stenosis following ingestion of

* Submitted for publication, Dec. 13, 1929.

* From the Departments of Pathology and Medicine, University of Illinois College of Medicine, and the Cook County Hospital Laboratories.

1. Halstead, A. E.: Pyloric Stenosis Following Sulphuric Acid Poisoning, Surg. Clin. Chicago **1**:495 (June) 1917.

2. Vinson, P. P., and Hartman, H. R.: Pyloric Obstruction Due to Swallowing Solution of Concentrated Lye, M. Clin. North America **8**:1037 (Jan.) 1925.

3. Vinson, P. P., and Harrington, S. W.: Cicatricial Stricture of the Stomach Without Involvement of the Esophagus Following the Ingestion of Formaldehyde, J. A. M. A. **93**:917 (Sept. 21) 1929.

acid or lye. That this experience is not unique is borne out by observations made elsewhere and recorded in connection with other phases of gastric disease. For instance, although mention of corrosive poisoning is not included in the index to Crohn's [4] book on diseases of the stomach, in the chapter on gastritis three cases of late corrosive lesions of the stomach are alluded to but are discussed from the standpoint of prognosis of gastritis.

Although gastric stenosis is not an infrequent sequel of corrosive poisoning, little information on the subject is available in our literature. One might conclude from this lack of information that gastric sequelae following corrosive poisoning possess no distinctive features and that each case is practically an entity in itself. That this conclusion is incorrect is indicated by the five cases to be reported, in each of which a characteristic syndrome can be readily identified.

REPORT OF CASES

CASE 1.—F. R., a white man, aged 41, entered the hospital, June 10, 1928, with the history of having been in good health until the day of entrance, when, shortly after his noon meal he swallowed nitric acid in mistake for liquor. Almost immediately, he experienced a burning sensation in the epigastrium, and within thirty minutes after ingestion he vomited an irritating fluid. On entrance to the hospital, he complained of persistent epigastric distress and vomiting after eating. Examination disclosed oral and pharyngeal corrosion and epigastric tenderness. Chemical analysis of the gastric washings showed the presence of nitric acid. The patient responded favorably to treatment and after four days refused to remain any longer in the hospital. He was warned of the possibilities of gastric stenosis and admonished to return at the beginning of symptoms of obstruction.

The patient was readmitted to the hospital on July 12, 1928. He stated that after leaving on June 14, he felt relatively well for about three weeks. During the week prior to his second entrance, he suffered from considerable epigastric pain and a burning sensation, vomiting of a projectile type and obstipation. On examination, epigastric prominence due to a distended stomach was readily outlined. There were no visible peristaltic waves. Moderate epigastric tenderness was elicited. A test aspiration performed on admission yielded 900 cc. of fluid with no free and 13 degrees of total acidity. On the following morning, after a night's fasting, 1,000 cc. of gastric contents was aspirated, this time showing 15 degrees free and 27 degrees total acidity. Roentgenographic examination (fig. 1) revealed a normal esophagus and a greatly dilated atonic stomach. Projecting from the lesser curvature was a nipple-like process which was interpreted as the pylorus drawn upward toward the cardia following cicatricial shortening of the lesser curvature. No barium was seen to leave the stomach during a protracted fluoroscopic observation.

Operation was advised and performed by Dr. Karl A. Meyer, who found that the pylorus was thickened, narrowed and distorted. A gastro-enterostomy was performed with difficulty, owing to the friability of the tissues. The patient

4. Crohn, B. B.: Affections of the Stomach, Philadelphia, W. B. Saunders Company, 1927, pp. 781-782.

developed pneumonia postoperatively and died. Permission for a postmortem examination was not granted.

Case 2.—I. P., a white man, 37 years of age, previously in good health, entered the hospital on June 6, 1928. He stated that four days prior to entrance, shortly after his evening meal, he swallowed some dilute sulphuric acid which he had mistaken for castor oil. He began to vomit within thirty minutes. A physician was called, who performed gastric lavage. When admitted, the patient complained of sore mouth and inability to swallow solids but no marked gastric distress. Examination revealed ulceration and sloughing of the lining of the

Fig. 1 (case 1).—Marked dilatation of the stomach due to obstruction at the outlet. The pyloric portion represented by the nipple-like projection has been drawn upward as a result of cicatricial shortening of the lesser curvature. The esophagus is normal.

mouth and pharynx. After the use of bland mouth washes and demulcents, the patient's symptoms disappeared. On June 12, 1928, he was discharged with instructions to return for observation and a warning of the possibility of gastric sequelae.

The patient reentered the hospital on July 2, 1928, with the complaint of constant gastric pain, acid eructations, vomiting and constipation. On examination, the epigastrium was prominent and tender and the borders of the stomach

easily outlined. Aspiration of the fasting stomach yielded 600 cc. of gastric contents which contained no free and 40 degrees of total acidity. The following morning, after an Ewald test breakfast, 650 cc. of material was removed with no free and 36 degrees of total acidity. Roentgenographic examination (fig. 2) demonstrated a normal esophagus and cardia. The pylorus was rigid, narrow,

Fig. 2 (case 2).—Anomalous deformity of the pyloric region and lesser curvature of the pars media due to acid corrosion. No roentgen evidence of abnormality of the esophagus is present.

deformed and elongated to measure more than 3 cm. Three small pockets protruded from the side of the lesser curvature in the distal portion of the stomach. The roentgenologic diagnosis of carcinoma of the pylorus was made with the reservation that a benign ulcer with extensive scarring might explain the roentgenographic appearance.

Laparotomy was performed by Dr. Karl A. Meyer, whose operative report reads: "The pyloric portion of the stomach is stenosed by a stricture which extends from a point 3 cm. proximal to the pylorus to involve the sphincter. There is scarring and puckering of the serosa over the pyloric region reaching for a distance of 6 cm. along the lesser curvature. The gastric mucosa is thickened, friable and bleeds easily." A posterior gastro-enterostomy was performed. Convalescence was uneventful, and the patient was discharged three weeks later, completely relieved of symptoms. The roentgenogram taken before discharge showed an adequately functioning gastro-enterostomy.

Fig. 3 (case 3).—Concentric cylindric stenosis of the distal two thirds of the stomach following corrosive poisoning. The barium within the esophagus is due to gastric regurgitation.

Case 3.—A. S., a robust white man, aged 57, entered the hospital on March 8, 1929. He stated that twenty-four hours prior to admission, as he was about to return home for his evening meal, he swallowed a liquid which tasted like acrid wine and which was offered to him as whisky. Immediately after swallowing the fluid, the patient experienced severe epigastric pain and numbness in the region of the mouth and pharynx. Severe vomiting ensued, which became bloody within a short time. General weakness associated with a cold sweat followed. The patient then drank a bottle of milk, which he quickly vomited. On entrance,

his complaints were pain in the epigastric and retrosternal regions and sore throat. On examination, the mucosa of the mouth, uvula and pharynx was seen to be covered by a white membrane which in places was ulcerated and hemorrhagic. The temperature was 102 F., the pulse rate 110, and the respiratory rate 25. The patient was given milk to drink, whereupon retching and vomiting occurred. The vomitus was sanguineous. Sedatives and mineral oil were administered and a cocaine spray prescribed to control the pain in the pharynx. The patient improved rapidly and expressed a desire to leave the hospital. He was informed of the frequent sequelae, both esophageal and gastric, and was advised to remain. He accepted the advice.

Fig. 4 (case 4).—Roentgen evidence of deformity of the duodenal cap and the pyloric zone resulting from ingestion of dilute lye on a full stomach.

On March 23, 1929, while under observation, he first complained of slight dysphagia. The difficulty in swallowing became progressively worse. On April 3, roentgenographic examination revealed an esophageal constriction just below the level of the cricoid cartilage and (fig. 3) a tubular constriction of the pars media and the pars pylorica of the stomach, with no peristalsis. Repeated esophagoscopic examinations showed a friable, polypoid mucous membrane which the esophagoscopist persisted in reporting as carcinoma. In view of the history and our previous experience with the polypoid hypertrophy and friability of the mucosa of the stomach shortly after corrosive poisoning, we were reluctant to

accept this diagnosis. A biopsy was therefore taken and a report of inflammatory hyperplasia returned by the pathologist. Esophageal dilatation readily overcame the subcricoid constriction observed in the roentgenogram, but nevertheless the patient complained of distress following ingestion of a moderate-sized meal. Consequently, small frequent feedings were prescribed, and the patient was ren-

Fig. 5 (case 4).—Stomach and first portion of duodenum opened along the lesser curvature. Had the stomach been opened along the greater curvature, the area of ulceration would be seen to be triangular with the apex toward the cardia. Note the islands of remaining mucosa near the greater curvature.

dered practically symptom-free. He was discharged on June 26, 1929, approximately three and a half months after admission, with the advice to return on the slightest indication of further stenosis.

Case 4.—E. B., a white man, 45 years of age, had been previously in good health but was unemployed and despondent. On July 11, 1929, he swallowed

half a tumbler of dilute lye in an attempt at suicide. He experienced severe epigastric burning, soreness of the throat and vomiting. The following day he entered the hospital, mainly on account of persistent emesis. On examination there were seen moderate injection and ulceration of the oral and pharyngeal mucosa. There was moderate epigastric tenderness. On treatment with liquid

Fig. 6 (case 5).—Atypical deformity of the pars pylorica consisting essentially of a filling defect and an addition shadow on the greater and lesser curvatures, respectively, due to acid corrosion.

petrolatum and a soft diet, the patient ceased vomiting and recovered satisfactorily. Roentgenographic examination (fig. 4) made on July 19, 1929, disclosed an irregular, rigid defect of the prepyloric, pyloric and duodenal regions, producing moderate obstruction. A roentgenologic diagnosis of carcinoma of

the stomach was made by the roentgenologist. This diagnosis was made despite the history, to which little credence was attached. On July 22, 1929, the patient committed suicide by hanging.

Through the courtesy of Dr. S. A. Levinson, the stomach and esophagus obtained at autopsy were placed at our disposal. Dr. Levinson's description is as follows: "The stomach has been opened along the lesser curvature (fig. 5). The esophagus and cardia are free from change. The rugae of the walls of the fundus and pars media and of practically the entire length of the greater curvature are normally prominent. The proximal two thirds of the lesser curvature is likewise practically normal, while in the distal third there is seen a triangular area of ulceration with the apex directed toward the cardia and the base ending abruptly just proximal to the pyloric ring. The stomach having been opened along the lesser curvature, the triangle is seen to be divided along its perpendicular. The area of ulceration is quite smooth, except for a few islands of mucosa which are retained, especially along the greater curvature side. The wall of the stomach in the involved area is firm and thick. The pyloric ring is thickened but free from ulceration."

Microscopic sections from the denuded area disclosed a complete loss of the mucosa and muscularis mucosae. There was a marked polymorphonuclear and round cell infiltration of the submucosa and muscularis. Sections from other parts of the stomach and from the esophagus showed no noteworthy change.

CASE 5.—D. B., a colored man, aged 33, was in good health until September 3, when, following a hearty evening meal, he drank approximately 4 ounces (118.29 cc.) of 12 per cent sulphuric acid, mistaking it for whisky. Immediately after drinking the acid, he hastened to the street, boarded a passing street-car, and after riding a few minutes experienced burning in the substernal and epigastric regions. He dismounted from the car, began to vomit, felt weak and fainted. He was brought to the Cook County Hospital, where he received gastric lavage and stimulants. He continued vomiting and suffering from epigastric pain for a few days, after which the pain disappeared. The vomiting, although it persisted, became less frequent and less profuse. The patient recovered his strength and at his request was released from the hospital on September 23, although he still experienced difficulty in retaining food.

He reentered the hospital on Oct. 1, 1929, complaining of persistent vomiting, epigastric cramps, weakness and loss of weight. From the history of an ingestion of acid on a full stomach, the presence of a pyloric obstruction due to cicatricial contraction was confidently predicted. The patient was given a glass of water, which he swallowed without difficulty and retained. The results of physical examination, except for epigastric tenderness, were negative.

Roentgenographic examination (fig. 6) on Oct. 3, 1929, showed an annular deformity of the pars pylorica of the stomach, which was rigid. The lesser curvature of the pars media was rigid and irregular. Operation performed the following day by Dr. V. L. Schrager revealed a contracted, thickened pars pylorica and an extensive fibrous perigastritis, especially along the lesser curvature. On account of the adhesions, the posterior wall could not be mobilized, and an anterior gastro-enterostomy was performed. The patient developed a subphrenic abscess which was surgically drained. A pyopneumothorax supervened and culminated in the patient's death. Autopsy was performed on Nov. 13, 1929, by Dr. J. J. Kearns, who demonstrated a tubular constriction of the pars pylorica and a high grade inflammation of the mucosa along the entire extent of the lesser curvature. There was no evidence of infection, old or recent, about the gastro-enterostomy site. The esophagus was normal.

COMMENT

In reviewing the cases described, one is struck by the uniformity in the sequence of events. The patient presents the symptoms and signs of recent corrosive poisoning, whereupon remedial measures are employed. The vomiting ceases more or less, the visible oral lesions disappear, and apparently the patient has recovered. As a consequence, he is discharged as cured or at least improved. Within a variable period, he returns with symptoms of obstructive vomiting, emaciation, and roentgen evidence of obstruction in the stomach alone or in combination with the esophagus. Although the clinical sequence of events is strikingly constant, the anatomic location and character of the lesions produced are variable. As will be seen later, the location and extent of residual involvement after corrosive poisoning are not purely accidental but are dependent on certain definite factors.

Factors Which Influence the Location and Type of Gastric Lesions.—Type of Corrosive: The type of corrosive used, whether acid or alkali, has an important bearing on the localization of the permanent damage. The escape of the esophagus, with exclusive involvement of the stomach, is seen most frequently in cases in which acid has been employed. An explanation of this fact is furnished by the work of Delore and Armand.[5] These authors showed that ordinary concentrations of acids during their rapid course through the esophagus have but a superficial scorching effect on the squamous epithelial lining. The simple columnar epithelium of the stomach is, however, readily corroded by similar concentrations of acids and this, combined with the longer duration of contact, leads to extensive damage. Lye, however, has a universally colliquative action, irrespective of type of tissue, so that esophagus and stomach are equally involved, the former more extensively, since dilution does not occur there. Orator,[6] in an analysis of thirty-four cases of late gastric sequelae following the ingestion of acid, mentioned only seven cases in which combined pyloric and esophageal stenosis took place. In the remaining cases, gastric lesions exclusively were found. Rieder,[7] Oeding,[8] Liebman[9] and others reported

5. Delore and Armand, quoted by Elisher, E.: Pylorusstenosen hervorgerufen durch Salzsäuren und Aetzlaugen, Zentralbl. f. Chir. **50**:165 (Feb. 3) 1923.

6. Orator, V.: Säurenverätzungen des Magens und Zinkdampschaden, Zentralbl. f. Chir. **56**:514 (March 2) 1929.

7. Rieder, W.: Pylorus Stenose infolge Mineralsäureverätzungen, Zentralbl. f. Chir. **56**:1049 (April 27) 1929.

8. Oeding, H.: Ein Fall von Pylorusstenose nach Salzsäureverätzung, Zentralbl. f. Chir. **53**:397 (Feb. 13) 1926.

9. Liebman, E.: Ueber einen Fall von Abgang der Magenschleimhaut durch dem Darm nach Vergiftung mit konzentrierter Salzsäure, München. med. Wchnschr. **64**:1292 (Oct. 2) 1917.

only pyloric stenosis as following the ingestion of acids. With alkalis, on the other hand, gastric strictures, when they occur, do so as a rule in combination with esophageal stenosis, as in the cases described by Vinson and Hartman,[2] Rochet and Barbier [10] and others. Heindl [11] in his review of 116 cases of stricture of the esophagus caused by lye found only 20 per cent associated with pyloric stenosis. Exclusive late involvement of the stomach after the taking of alkali is rare. A case described by Elisher [12] in which six months following the ingestion of lye only pyloric stenosis was found, and our case 4, in which the only demonstrable lesion was gastric, are worthy of note.

Concentration of Corrosive: The concentration of the corrosive does not play the important rôle one might expect. The highly concentrated poisons cause perforation and early death and therefore do not concern us here. In general, the alkalis are taken in the form of lye; the acids, in the commercially employed strengths. However, no concentration of corrosive, regardless of how dilute, is to be considered innocuous. It is particularly with low concentrations which have little or no effect on the esophagus and which are longest tolerated within the stomach, that extensive gastric changes are produced. Sick [13] reported a case of pyloric stenosis following the ingestion of a small amount of dilute acid and demonstrated experimentally the importance of dilute corrosive in producing extensive gastric damage.

Location and Type of Lesion.—When a group of patients presenting late permanent changes within the stomach are studied, it is seen that the location and extent of the lesions vary. A pyloric stenosis, a tubular narrowing of the antrum and pylorus, an hour-glass constriction, concentric constriction of the pars pylorica and pars media, a leather bottle type of deformity or various combinations of these lesions are encountered. Again the scarring is thin or heavy, localized or universal, focal or diffuse. The different types of structural change are fully discussed by Merkel [14] in his comprehensive treatise on the pathologic

10. Rochet, P., and Barbier, J.: Stenose cicatricielle oesophagienne et pylorique a la suite d'une ingestion de liquide caustique, Lyon chir. **24**:405 (July-Aug.) 1927.

11. Heindl D.: Klinische Beobachtungen an 137 gutartigen Oesophagusstenosen der I Chirurgische Universitätsklinik, Wien., 1901-1925, Ztschr. f. Chir. **199**:252 (Nov. 1) 1926.

12. Elisher, E.: Pylorusstenosen hervorgerufen durch Salzsäuren und Aetzlaugen, Zentralbl. f. Chir. **50**:165 (Feb. 3) 1923.

13. Sick, K.: Klinische, experimentelle und histologische Untersuchungen über Säurevergiftung des Magens, Deutsches Arch. f. klin. Med. **148**:318 (Oct.) 1925.

14. Merkel, H.: Die Magenverätzungen, in Henke, T., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1, pp. 219-315.

anatomy of corrosive action on the stomach. The question naturally arises, what determines the localization and extent of the defect which affects the stomach? The explanation involves a knowledge of the physiology of gastric reception of food and fluids.

As early as 1905, Grützner [15] demonstrated by means of various colored foods that within the fundus stratification and storage occur. Cohnheim [16] in 1907 demonstrated the rapidity with which fluid ingested on a full stomach appears almost unchanged in the duodenum tapped by an artificial fistula. Later Waldeyer [17] and Aschoff [18] presented the idea of a "Magenstrasse," a conception according to which the lesser curvature acts as the pathway for rapid progress of fluid from the esophagus to the pylorus without the admixture of food and also as the passageway for well triturated food from the stomach into the duodenum. The work of Waldeyer and Aschoff furnished a logical basis for Grützner's [15] and Cohnheim's [16] observations and also an explanation for the type and localization of gastric lesions following corrosive poisoning.

In the full stomach, the ingested corrosive fluid is rapidly passed through the esophagus along the lesser curvature to the pylorus where it spreads out in triangular fashion with the base toward the pylorus and the apex toward the cardia (see fig. 5). There occurs a pylorospasm which halts the further progress of the fluid, and the contraction of the stomach renders the lesser curvature very short. The corrosive is in contact with the mucosa of the pylorus and lesser curvature on the one side and with food on the other. The latter has diluting and neutralizing effects. Within a short interval, vomiting takes place, ridding the stomach of the corrosive, but leaving a raw ulcerated lesser curvature and pars pylorica where toxic and perhaps bacterial gastritis may supervene. The predetermined strictural changes are stenosis of the pylorus with scarring of the lesser curvature and some degree of antrum involvement (figs. 1, 2, 4 and 6). With acids, these changes occur alone; with alkalis, usually in combination with esophageal strictures.

In the empty contracted stomach, on the other hand, the lesser curvature is almost vertical, and the stomach forms a funnel (Kaufmann [19]) with the antrum and pylorus constituting the deepest portions.

15. Grützner, P.: Ein Beitrag zum Mechanismus der Magenverdauung, Arch. f. d. ges. Physiol. **106**:463 (Feb.) 1905.

16. Cohnheim, O.: Beobachtungen über Magenverdauung, München. med. Wchnschr. **54**:2581 (Dec. 24) 1907.

17. Waldeyer, W.: Die Magenstrasse, Sitzungsber. d. k. Preuss. Akad. d. Wissensch. **29**:595, 1908.

18. Aschoff, L.: Ueber den Engpass des Magens, Jena, Speyer & Kerner, 1908.

19. Kaufmann, E.: Spezielle pathologische Anatomie, ed. 7 and 8, Berlin, W. de Gruyter & Company, 1922, vol. 1, pp. 529-533.

The ingested liquid comes in universal contact with the gastric mucosa, but remains longest in contact with the pars pylorica and pars media because pylorospasm prevents further progress onward of the corrosive, while the air above the fluid diminishes the extent of contact with the fundus. Hence, although vomiting occurs much earlier with the empty than with the full stomach, dilution and absorption of the corrosive and protection of the mucosa by food are absent. As a result extensive ulceration and damage occur. If perforation and death do not ensue, there results complete pyloric and antrum constriction, with simultaneous narrowing of the pars pylorica and pars media (fig. 3), total gastric scarring (linitis plastica) or hour-glass stenosis due to antrum spasm.

Actual data as to the condition of the stomach, whether full or empty prior to the ingestion of the poison, are meager. Although many authors (Shinz,[20] Elisher,[12] Merkel,[14] Galdau and Pop[21] and others) emphasized the importance of the state of the stomach, only few offered specific information with reference to this point. Elisher[12] recorded the condition of the stomach in his own cases and suggested the view expressed here. In cases 1, 2 and 5 of our series, the corrosive was swallowed after eating, and in each case a pyloric stenosis with scarring of the lesser curvature resulted. The patient in case 3 ingested the poison on an empty stomach just before going home for his evening meal; in this case, extensive constriction of the pars pylorica and pars media was produced. In case 4, no information was recorded regarding the state of the stomach at the time the lye was ingested. From the type of lesion produced it is reasonable to assume that the stomach was empty.

Clinical and Roentgenographic Aspects of Gastric Sequelae of Corrosive Poisoning.—The interval that elapses between the ingestion of the corrosive and the development of the gastric stricture is variable. The usual period is from one to six months. According to published reports, the time interval most frequently is from three to four weeks, as occurred in most of our cases. The gastric sequelae may not, however, progress to the point of giving symptoms for several years after the swallowing of the poison. Thus Galdau and Pop[21] cited two instances of the ingestion of alkali in each of which an early esophageal constriction was overcome by dilatation, with apparent recovery, but was followed in three years in one and in six years in the other case by vomiting. Roentgenograms revealed obstructive deformities of the

20. Shinz, H. R.; Baensch, W., and Friedl, E.: Lehrbuch der Roentgendiagnostik, Leipzig, 1928, pp. 926-927.

21. Galdau, D., and Pop, A.: Die postkaustischen Magenverätzungen, Fortschr. a. d. Geb. d. Roentgenstrahlen **37**:705, 1928.

antrum and pylorus in both patients. Assmann [22] reported a case of pyloric stenosis which occurred nine years after corrosive poisoning.

The two cases of Galdau and Pop, as well as one described by Orator,[6] illustrate an interesting series of events. The initial symptoms of corrosive poisoning may be followed after an interval by evidences of obstruction of the esophagus or cardia. Following relief of the esophageal or upper gastric stricture, another obstruction, lower in the stomach, may develop. Orator described a case of stenosis of the cardia which followed one month after the ingestion of hydrochloric acid and for which gastrostomy was performed. The result was satisfactory for eight days; then regurgitation through the fistula made it evident that a pyloric stenosis had supervened. A jejunostomy performed for relief ended fatally.

The clinical picture presented by the gastric sequelae varies only in detail. Epigastric pain and vomiting are universal. The pain is usually mild, and is dependent on the disturbance in motility. A sense of pressure and fulness after meals, relieved by vomiting, is most frequent. At times, especially with lesser grades of obstruction, epigastric cramps of moderate severity are experienced. Vomiting is by far the most obstrusive and most persistent symptom. It follows immediately to several hours after the taking of food. The vomitus may contain, in addition to undigested food, blood, pus, lactic acid and Oppler-Boas bacilli. Hydrochloric acid is generally absent or if present is low in amount, as in case 1 of our series. The secretory and motor disturbances produced by corrosives may be maintained, as emphasized by Sick,[13] over a long period of time. This investigator, although unable to reproduce strictures in his animals, noted decreased motility and secretion for months after the corrosive was administered.

The patient presents physical evidence of emaciation and dehydration of varying degree. The abdomen may be scaphoid, but frequently the stomach produces an epigastric fulness due to gastric tonicity or distention with at times visible peristalsis. Even in cases in which a concurrent esophageal stenosis exists, providing it is incomplete, prominence of the epigastrium with peristaltic waves may be seen rather than the expected scaphoid abdomen. This paradoxic combination of esophageal obstruction and gastric distention was first described in a case reported by Rochet and Barbier.[10]

From the clinical data alone obstruction high in the gastro-intestinal tract is readily diagnosed. The roentgenogram employed for more accurate diagnosis reveals a variety of structural and functional changes.

22. Assmann, H.: Klinische Roentgendiagnostik der inneren Erkrankungen, ed. 3, Leipzig, F. C. W. Vogel, 1924, pp. 473-475.

Pyloric stenosis, pyloric and antral constriction, rigid cylindric narrowing of the pars pylorica and pars media, hour-glass constriction or total gastric contraction, alone or in combinations or in association with esophageal strictures, is encountered.

Deformities of the stomach resulting from corrosive poisoning as shown by the roentgen ray are often mistaken for other lesions, particularly for carcinoma and ulcer. The summaries of Galdau and Pop [21] of eight of their own cases and thirteen from the literature illustrate the difficulties in radiologic diagnosis. These authors described particularly one case in which pain and vomiting led to a roentgen examination, which revealed a rigid, narrow antrum and pylorus. A roentgenologic diagnosis of carcinoma was made. The deformity, however, was due to cicatricial contraction occasioned by the ingestion of alkali six years prior. Schinz [20] and Assmann [22] mentioned similar experiences. In case 1 of our series, the roentgen diagnosis of ulcer with stenosis was made, and in cases 2 and 4 the roentgen interpretation was gastric carcinoma. Differentiating features mentioned by various authors, such as the greater delicacy and more linear contour of the corrosive lesions, may be of some help, but generally are not dependable. Multiplicity of lesions, on which the correct diagnosis was based in case 3, is highly suggestive.

The changes in motility as observed roentgenologically are also variable. A review of the recorded observations and of our own shows that all variations occur, from huge, atonic dilated stomachs with absence of peristalsis, as in case 1 of our series, to small, contracted stomachs with hypermotility, as in case 3. Spasm at the site of injury especially early is a prominent feature, as demonstrated by Liebman,[9] who roentgenologically followed a case of poisoning throughout its course. He found a sickle-shaped, contracted stomach five days after ingestion of the corrosive, which later resumed the normal gastric outline, except in the region of the pylorus, where permanent stenosis occurred.

A consideration of the roentgen appearances of the gastric sequelae of corrosive poisoning points to the conclusion that the history is of utmost importance in arriving at a roentgenologic diagnosis. The difficulty of distinguishing a cicatricial from a neoplastic deformity on the basis of the roentgen observations alone and the influence which the anamnesis exerts on the roentgenologist's opinion are exemplified by the following case:

On May 19, 1929, a colored man, 38 years of age, ingested what was alleged to be lye and immediately afterward experienced severe abdominal pain. He vomited a clear material after a few minutes. This was followed by frank blood. About one hour later, the hematemesis was repeated in the hospital examining-room. He was sent to the roentgenologic department with a definite diagnosis

of corrosive poisoning. The roentgenogram, taken June 16, 1929, showed an irregular filling defect of the prepyloric region with obstruction. The roentgen diagnosis was corrosive cicatrization of the prepyloric area. The exploratory operation revealed an extensive carcinoma of the prepyloric region involving also the perigastric lymph glands. Subsequent investigation disproved the original history and showed that the material ingested was milk of magnesia.

Treatment.—The treatment of gastric sequelae is usually surgical. Occasionally, the medical management succeeds, particularly in cases in which the obstruction is due wholly or in part to spasm or active inflammatory processes which recede. Sick,[13] for instance, treated a patient with corrosive pyloric stenosis for six months expectantly, and recovery ensued without operation. The type of operation may vary according to the time that elapses following the initial accident. In the late cases, gastro-enterostomy is the operation of choice. In the early cases, Rieder,[7] among others, advises preliminary jejunostomy to permit the stomach to rest and the gastritis to subside. Our experience with case 5 supports the idea that gastro-enterostomy in the presence of an active inflammation may prove disastrous and should be postponed. Combination stenoses present special problems.

CONCLUSIONS

1. The ingestion of acid even in relatively small quantities or low concentrations may be followed by stenosis of some part of the stomach without esophageal involvement.

2. The swallowing of lye leads to esophageal obstruction associated frequently with gastric obstruction, rarely to gastric obstruction alone.

3. Organic obstruction of the stomach does not occur immediately, but usually manifests itself several weeks after recovery from the initial effects has been considered complete.

4. Late gastric stenosis should be anticipated in all cases of corrosive ingestion (especially when the substance is known to be an acid), even though the patient is restored to complete health shortly following the poisoning.

5. The type and location of the lesion in the upper part of the gastro-intestinal tract can be predicted from a knowledge of the corrosive ingested, whether acid or alkali, and the state of the stomach, whether empty or full.

6. In late cases of cicatricial stenosis of the stomach, gastro-enterostomy is the operation of choice. In early cases in which an active inflammation exists, a preliminary jejunostomy is often advisable.

Book Reviews

HYPERTENSION AND NEPHRITIS. By ARTHUR B. FISHBERG, M.D., Adjunct Attending Physician to Mount Sinai and Montefiore Hospitals, New York. Price, $6.50. Philadelphia, Lea & Febiger, 1930.

This book is intended for the general practitioner, yet it is undoubtedly the best work in its field in English, not only from a practical clinical standpoint, but as a clear, critical, extremely well balanced digest of the literature on the many pressing problems of Bright's diseases. The author has contributed personally, in no small degree, toward the solution of some of these problems so that one appreciates, all the more, the direct frankness with which he disposes of the chaff and the unnecessary tags and ends passing ordinarily as scientific work. The chief aim of the author seems to be simplicity, whether he is discussing renal function tests, pathology, classification of Bright's diseases or treatment. Nowhere, however, does this simplicity replace the completeness of important details. It consists largely in the careful separation of essentials from nonessentials. Hence the book is a true quintessence of all the important factual and theoretical content of our knowledge of Bright's diseases.

The title at once indicates the author's credo—"Hypertension and Nephritis"—two separate groups of diseases, yet somehow interrelated. The arrangement is admirable, proceeding from a discussion of disturbed renal function and its consequences to tests of renal function, the four cardinal aspects of Bright's diseases—albuminuria (and cylindruria), edema, uremia and arterial hypertension with all its sequels—and the subdivisions of Bright's diseases, i. e., the nephroses, nephritides and essential hypertension. The large apportionment of space to acute glomerulonephritis and to essential hypertension seems very wise in view of the keystone positions of these two conditions.

The author constantly stresses the unitary nature of impairment of renal function, that is, the loss of concentrating power regardless of the substance considered. Cushny, Starling and Richards are not mentioned in the chapter on pathologic physiology. Is the gap between the normal and pathologic physiology of the kidneys completely unbridgable? Most of the renal function tests, including metabolic balance studies, are shown to be unnecessary or useless while the author's simplified concentration or specific gravity test is preferred for clinical work. The distinction between renal impairment detectable by concentration tests and renal insufficiency as shown by nonprotein nitrogen retention in the blood is clearcut. The author describes in detail the urea clearance test of Van Slyke and his associates but fails to understand the difference between it and the Ambard constant, and questions its superiority over his own test without giving any comparative studies. The simple specific gravity test, however, may be easily carried out by the general practitioner and can give him a surprisingly accurate index of renal function.

Albuminuria is attributed to glomerular changes rather than to biologic alteration of the plasma proteins. Nephrotic edema is explained on the mechanical basis so richly supported by the clinical and experimental work of the last thirty years. The author's review of this work is brief but masterly. Acute nephritic and cardiac edemas are properly separated out. A primary rôle of the tissues in edema is ruled out on the grounds of lack of convincing evidence. The treatment for edema includes the best available information, stripped of all encumbrance. Nowhere in the literature on edema will a better chapter than this one be found.

Uremia is defined as a complex autointoxication resulting from the summation of the effects of retention of the various urinary constituents. The clinical picture is clearly delineated, the diagnosis made precise and the treatment sanely grounded.

In the chapter on arterial hypertension emphasis is laid on the relative nature of normal blood pressure and the factors underlying it. The pathologic anatomy

of hypertension is a field peculiarly the author's own province and is admirably sketched. Throughout this part precise definition of pathologic concepts is resorted to, thus making a complex subject much more intelligible. The unique distribution of arteriosclerosis in various organs, the lack of evidence of the systemic nature of this process, the relationship to age and the rôle of this vascular disease as a sequel to hypertension are some of the important items discussed. The mechanism of cardiac dilatation and insufficiency is frankly admitted to be unknown. The pathogenesis of arterial hypertension is exhaustively considered. The author leans toward the teleologic theory of renal hypertension and the concept of widespread functional vasoconstriction in all forms of hypertension of long duration. He contradicts himself somewhat on page 189, when speaking of hypertension as only a symptom and later of essential hypertension as a disease. Hypertensive encephalopathy is very well discussed from every angle. It is clearly separated from true uremia and closely related to eclampsia and lead encephalopathy. Cerebral vascular spasm is given the leading rôle, with edema a secondary and inconstant position. Hypertensive retinitis is adequately described except for insufficient analysis of the relationship of retinal arteriosclerosis to the ophthalmoscopic observations.

The classification of Bright's diseases is essentially a modernized version of the Volhard and Fahr system, with substitution of essential hypertension for benign and malignant nephrosclerosis and inclusion of benign albuminurias, multiple glomerular embolization and the senile arteriosclerotic kidney in individual rubrics.

The nephroses are defined from the original anatomic point of view and then subdivided. Mercurial nephrosis is briefly but sufficiently reviewed. The subject of chronic nephrosis is skilfully treated. The sequence of albuminuria, reduced plasma proteins, edema and lipemia is developed with perfect clarity. A combination of the renal and metabolic theories of pathogenesis is favored, with the interesting suggestion that nephrosis may be a collective concept for several distinct diseases. The treatment for chronic nephrosis, as detailed by the author, can scarcely be improved.

The important subject of acute glomerulonephritis is exceedingly well treated. The discussion of etiology, pathology and pathogenesis is second to none in the literature. The author differentiates sharply between diffuse and focal forms. The clinical picture is complete. The treatment meets each indication squarely and disposes of many outworn notions.

Chronic glomerulonephritis is logically developed from the acute type and given the same thorough analysis. The anatomic picture is enriched by the author's experience with the various types of arterial lesions. The variegated clinical features stand out distinctly to give an actual concept of the disease as a whole. Treatment, again, is splendidly considered. Throughout, the author's clinical maturity and sound judgment predominate.

Essential hypertension is admitted as a cloak for ignorance in analogy with the old term "pseudoleukemia." The pathology secondary to hypertension is, as usual in this book, excellently outlined. The "malignant phase" is defined on the basis of arteriolonecrosis and endarteritis and acutely progressive renal insufficiency. If accepted, this definition should materially reduce the clinical incidence of malignant hypertension. The gross and microscopic picture of the malignant phase is excellently portrayed. In further chapters the various factors involved or claimed to be important in the pathogenesis of hypertension are discussed. Endocrine etiology is ruled out except in the case of the suprarenal tumors, and even there the mechanism is still in the realm of mere speculation. "There are few fields in medicine in which ignorance is more profound," p. 441. High protein diet is discarded as a significant cause. Obesity, gout, alcohol, salt, tobacco, cholesterol, intestinal intoxication, etc., are all put in their proper place—the first two as constitutional associates of hypertension and the rest as hard-ridden medical hobbies. Emotional and mental factors are not credited with the capacity of causing hypertension but are considered important accessories. On the whole, according to the author, an inherited constitutional predisposition is the fundamental basis of essential hypertension. It takes courage to state that no effect was ever seen on the

blood pressure from the removal of infected teeth, tonsils or other foci of infection. The whole clinical syndrome, with the important cardiac manifestations—including angina pectoris and cardiac asthma, the nervous symptoms, renal function, the changes in the eyegrounds, etc.—are all thoroughly and accurately rendered. Diagnostic difficulties are met and defeated. Prognosis is given. The treatment is at the same time ancient and modern; ancient in its philosophy of "moderation in all things" and modern in its meticulous detail. Nothing of value has been left out; nothing irrational has been included.

Finally, comes a rather sketchy discussion of renal and hypertensive disease in pregnancy, a field obviously not within the author's own experience. This chapter is somewhat of an anticlimax.

Minor errors in typography and the spelling of authors' names will undoubtedly be corrected in future editions. The illustrations are satisfactory. This book by Fishberg meets the crying needs of the practicing physician, the medical student and the clinical teacher and investigator. It is a landmark in American medical publication.

DIAGNOSTISCHE UND THERAPEUTISCHE IRRTÜMER UND DEREN VERHÜTUNG—INNERE MEDIZIN; ERSTES HEFT, KRANKHEITEN DES STOFFWECHSELS. ZWEITE, VOLLKOMMEN NEU BEARBEITETE AUFLAGE. VON PROFESSOR DR. S. ISAAC, Dirigierender Arzt der Inneren Abteilung des Krankenhauses der Israelitischen Gemeinde in Frankfurt a. M. Price, 10 marks. Pp. 150. Leipzig: Georg Thieme, 1929.

A condensed but complete and readable review of certain metabolic diseases is presented in this second edition under the title given. Of the conditions dealt with by the author, obesity and diabetes mellitus are given the largest amount of space and by far the best handling. From the point of view of the general practitioner, to whom the book is addressed, it would be difficult to find a saner or more helpful discussion of the theoretical and practical problems involved in the diagnosis and treatment of obesity and diabetes mellitus. Undernutrition, diabetes insipidus and gout are also taken up. The large clinical experience of the author and his familiarity with the literature, combined with good judgment in therapeutics, make this book a valuable reference for the practicing physician. Translation into English would seem desirable.

HANDBUCH DER ERNÄHRUNGSLEHRE. BAND II: SPEZIELLE DIATETIK DER KRANKHEITEN DES VERDAUUNGSAPPARATES. TEIL I: MAGEN. By CARL VON NOORDEN, Frankfort-on-Main and HUGO SOLOMON, Buenos Aires. Price, 39 marks. Pp. 460. Berlin: Julius Springer, 1929.

This is a portion of an encyclopedia of clinical medicine compiled by Langstein, von Noorden and Schittenhelm. It is typically German in its thoroughness. If one desires a reference book wherein one may find a consideration of all treatments ever recommended for any gastric condition, this work fills the requirement. It is complete. For any other purpose, however, such a compilation is of little value. The treatment of gastric disorders is neither as complicated nor as difficult as this volume would indicate. The known facts of gastric therapy as related to recognizable gastric disease could be given in fewer pages.

THE BABY'S FIRST TWO YEARS. By RICHARD M. SMITH, M.D. Price, $1.75. Pp. 159, with illustrations. Boston: Houghton Mifflin Company, 1930.

This manual answers the majority of questions that perplex the young inexperienced mother in the care of her baby. It is brief, clear and well written.

The first part deals with the development of the baby, breast and bottle feeding, the care of the body, habits and training and clothing. One chapter is devoted to the sick baby. In the second part, the baby's entire daily routine is outlined in minute detail and offers a great many valuable suggestions.

The third part is devoted to charts for recording the baby's progress, and a few simple recipes are given.

Among the many books written for mothers on the care of infants, this ranks among the best.

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, Editor-in-Chief, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $7.00; Canadian, $8.50; foreign, $9.50. Single copies, 25 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $12.00; Canadian, $12.50; foreign, $12.75.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

THE VALUE OF ACID NEUTRALIZATION IN THE TREATMENT OF GASTRIC AND DUODENAL ULCERS. WALTER LINCOLN PALMER, M.D., CHICAGO 165

LABORATORY STUDIES IN EPILEPSY. JOSEPH FELSEN, M.D., NEW YORK 180

BRONCHIAL ASTHMA: THE SEVERE CHRONIC INTRACTABLE TYPE. I. S. KAHN, M.D., SAN ANTONIO, TEXAS 218

ARTERIAL HYPERTENSION: EVALUATION OF THE PROGNOSIS. EDWARD J. STIEGLITZ, M.D., CHICAGO 227

PLASMA PROTEINS. H. J. WIENER, M.D., AND R. E. WIENER, PH.D., NEW YORK 236

POSTOPERATIVE RESULTS IN TOXIC GOITER. NORMAN E. CLARKE, M.D., AND IRENE BLACK, DETROIT 266

POSTMORTEM BLOOD CHEMISTRY IN RENAL DISEASE. S. H. POLAYES, M.D.; E. HERSHEY, M.D., AND M. LEDERER, M.D., BROOKLYN 283

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS: I. CONCENTRATION OF NON-PROTEIN NITROGENOUS CONSTITUENTS IN THE BLOOD. A. MAURICE WAKEMAN, M.D., AND CLARE A. MORRELL, M.A., NEW HAVEN, CONN. 290

FATAL HUMAN ANAPHYLACTIC SHOCK: REPORT OF A CASE, WITH AUTOPSY OBSERVATIONS AND REVIEW OF THE LITERATURE. JESSE G. M. BULLOWA, M.D., AND MENDEL JACOBI, M.D., NEW YORK 306

THE INFLUENCE OF A SPECIAL BREAKFAST ON THE BASAL METABOLISM OF PATIENTS WITH A PATHOLOGIC CONDITION. CHI CHE WANG, PH.D., AND JEAN E. HAWKS, M.S., CHICAGO 316

THE INTERMEDIATE METABOLISM OF FOREIGN SUGARS. ELLA H. FISHBERG, M.D., AND B. T. DOLIN, M.A., NEW YORK 321

EPIGASTRIC PULSATION: CLASSIFICATION IN REGARD TO THE FORM OF THE EPIGASTRIOGRAM. NOBUTATSU FUKUI, M.D., TOKYO, JAPAN 333

GASTRIC SEQUELAE OF CORROSIVE POISONING. WILLIAM S. BOIKAN, M.D., AND HARRY A. SINGER, M.D., CHICAGO 342

BOOK REVIEWS 358